UNITED STATES DISTRICT COURT

DISTRICT OF NEW JERSEY

OTSUKA PHARMACEUTICAL, CO., LTD., Plaintiff, v. SANDOZ, INC., TEVA PHARMACEUTICALS USA, INC., TEVA PHARMACEUTICAL INDUSTRIES, LTD., BARR LABORATORIES, INC., BARR PHARMACEUTICALS, INC., APOTEX, INC., APOTEX CORP., SUN PHARMACEUTICAL INDUSTRIES, LTD., SYNTHON BV, SYNTHON PHARMACEUTICALS, INC., and SYNTHON LABORATORIES, INC., Defendants.	Case No. 07-cv-1000-MLC-LHG 402 East State Street Trenton, NJ 08608 October 21, 2010 9:28 a.m.

TRANSCRIPT OF HEARING
BEFORE HONORABLE MARY L. COOPER
UNITED STATES DISTRICT COURT JUDGE

A P P E A R A N C E S:

For the Plaintiff: Finnegan, Henderson, Farabow, Garrett & Dunner, LLP
By: PAUL W. BROWNING, Ph.D.
JAMES B. MONROE, ESQ.
MICHAEL J. FLIBBERT, ESQ.
901 New York Avenue, NW
Washington, D.C. 20001

Fitzpatrick Cella Harper & Scinto
By: JOHN D. MURNANE, ESQ.
1290 Avenue of the Americas
New York, New York 10104

Court Reporter: Jomanna DeRosa
Job #33016

A P P E A R A N C E S (Cont'd.):

For Defendants Teva and Barr:
Kenyon & Kenyon, LLP
By: ELIZABETH HOLLAND, ESQ.
MARIA LUISA PALMESE, ESQ.
PETER L. GIUNTA, ESQ.
One Broadway
New York, New York 10004

Lite DePalma Greenberg, LLC
By: MAYRA V. TARANTINO, ESQ.
Two Gateway Center, 12th Floor
Newark, New Jersey 07102

For Defendant Apotex:
Husch Blackwell Sanders, LLP
By: DANIEL R. CHERRY, ESQ.
STEVEN E. FELDMAN, ESQ.
JAMES P. WHITE, ESQ.
120 South Riverside Plaza, Ste 2200
Chicago, Illinois 60606

Flaster Greenberg
By: JEFFREY A. COHEN, ESQ.
1810 Chapel Avenue West
Cherry Hill, New Jersey 08002

THE COURT: Good morning, everyone. Everyone may be seated except those who will state their appearances, and you may do so now.

MR. MONROE: James Monroe, Finnegan Henderson, on behalf of Otsuka Pharmaceuticals.

MR. FLIBBERT: Mike Flibbert of Finnegan on behalf of Otsuka.

MR. BROWNING: Paul Browning, also of Finnegan, also on behalf of Otsuka.

MR. MURNANE: John Murnane, Fitzpatrick Cella, on behalf of Otsuka.

MS. HOLLAND: Elizabeth Holland of Kenyon & Kenyon on behalf of the Teva and Barr defendants.

MS. PALMESE: Maria Palmese of Kenyon & Kenyon on behalf of Teva.

MR. GIUNTA: Peter Giunta of Kenyon & Kenyon on behalf of Teva and Barr.

MR. FELDMAN: Steven Feldman of Husch Blackwell on behalf of the Apotex defendants.

MR. CHERRY: Daniel Cherry, Husch Blackwell, for Apotex.

MR. WHITE: James White, Husch Blackwell, on behalf of the Apotex defendants.

MR. COHEN: Good morning, Your Honor. Jeffrey Cohen from Flaster Greenberg on behalf of the Apotex defendants.

MS. TARANTINO: Good morning, Your Honor. Mayra Tarantino from Lite DePalma Greenberg, also on behalf of Teva and Barr.

THE COURT: Welcome.

Welcome back to our excellent court reporter. Thank you.

So I suppose defendants will go first?

MS. HOLLAND: Yes, Your Honor.

THE COURT: Do you want to take up this motion to strike now or later?

I think I'd rather do it later. I have looked it over, and you can make your comments as you go along. I'll let you get to the meat of your presentation.

MS. HOLLAND: Thank you, Your Honor. Counsel for Otsuka and I have discussed this, and I think along the lines of what Your Honor said, Otsuka is, during its closing argument -- at the end of its closing argument, going to address the motion to strike. And then we will, during our rebuttal, respond to that.

THE COURT: That's fine.

MS. HOLLAND: So having said that, we would like to reserve some time for rebuttal.

THE COURT: Of course.

MS. HOLLAND: Thank you.

THE COURT: And you're not on a clock here anyway,

within reason.

MS. HOLLAND: Thank you. Your Honor, I'm going to be addressing the issues of double patenting and inequitable conduct, and then Mr. Feldman is going to address the issue of obviousness.

As Your Honor heard at trial, Otsuka obtained two patents covering the compound aripiprazole. That fact is not disputed. Otsuka's earlier '416 patent contained claims that covered the compound aripiprazole, and Otsuka actually used the '416 patent to keep others off the market with competing aripiprazole products. None of that is disputed.

It's also undisputed that the '416 patent, in addition to covering aripiprazole, covered billions of other carbostyril derivatives. And by claiming this whole class of compounds, Otsuka was able to keep other researchers from investigating them and their potential as antischizophrenic drugs.

The follow-on, the '528 patent, which is the patent-in-suit in this case, is exactly what the doctrine of double patenting was meant to prevent. It was meant to prevent the unjustified timewise extension of the right to exclude. And that is a quote from the Eli Lilly vs. Barr case.

Double patenting, its adoption, that's grounded in public policy and as the Federal Circuit found in the

In re Longi case, which we cited in our conclusions of law:

"The public should be able to act upon the assumption that upon the expiration of the patent, it will be free to use not only the invention claimed in the patent, but also modifications or variants which would have been obvious to those of ordinary skill in the art."

So the double patenting analysis here is very straightforward. Under the Federal Circuit law the Court must compare the asserted claims in this case to the claims of Otsuka's earlier '416 patent; in this case, Claim 13 of the '416 patent, which is the unsubstituted butoxy compound.

Otsuka's principal argument in this case is that a person of ordinary skill in the art would not have chosen the unsubstituted butoxy as a lead compound.

But that argument, Your Honor, is completely irrelevant to obviousness -- to obviousness-type double patenting. That argument only goes to the issue of obviousness.

The Court, when it's looking at double patenting, is required to start with the unsubstituted butoxy. That's just one of several differences between double patenting and obviousness.

Can we see closing slide 1.

This is from the Federal Circuit's recent decision, 2009. This is a quote from the Federal Circuit's 2009

decision in the Procter & Gamble case. And the Court was very clear that there were three distinctions between obviousness and double patenting.

The first is the one I just discussed, which is the fact that in a double patenting analysis, it's not the prior art that's being compared to the claim. It's the claim in the earlier patent; in this case, the Claim 13 of the '416 patent, which is the unsubstituted butoxy. That must be the starting point.

Second, in a double patenting analysis, the issue of motivation to modify the prior art is not a relevant consideration.

Finally, for double patenting, secondary considerations of nonobvious or so-called objective criteria of nonobviousness are also not relevant to double patenting.

Because of these differences, double patenting and obviousness are distinct defenses, and they have to be analyzed separately.

So on double patenting there is really only one question for the Court to answer: Is aripiprazole an obvious variant of the unsubstituted butoxy?

In other words, would a person of ordinary skill in the art, based on what was known in the prior art at the time, have considered aripiprazole to be obvious in light of the unsubstituted butoxy, Claim 13 of the '416 patent?

Can we see closing slide 2, please.

These are the structures of aripiprazole and the unsubstituted butoxy. Aripiprazole -- as Your Honor heard at trial, an aripiprazole molecule has formed parts. We have the carbostyril core.

THE COURT: Do you want that model that is in evidence? If you do, you can ask us to bring it out.

MS. HOLLAND: Thank you very much, Your Honor.

The aripiprazole molecule has a carbostyril core. It has a linker; in the case of an aripiprazole, a butoxy linker. It has a piperazine group and it has -- I'm sorry -- a phenyl ring.

The unsubstituted butoxy has these same four components to it, and in fact, it is identical to aripiprazole except for the phenyl ring. There is a phenyl ring on the unsubstituted butoxy.

Aripiprazole has chlorines at the 2- and 3-position of the phenyl ring. And the unsubstituted butoxy, as the name implies, is unsubstituted, or in other words, has hydrogens at those positions.

The structural similarity that you can see here, Your Honor, between the aripiprazole and the unsubstituted butoxy makes aripiprazole what is called prima facie obvious.

In other words, under the case law, because of the structural similarity, there's a presumption that

aripiprazole is obvious in light of the unsubstituted butoxy.

But we have much more in this case than just a presumption, as Your Honor heard at trial. The Nakagawa declaration contains data that would direct the person of ordinary skill in the art to take the unsubstituted butoxy and put chlorines at the 2- and 3-positions.

As Your Honor heard, the Nakagawa declaration was submitted during prosecution of the '416 patent by Otsuka in order to prove to the patent office that the compounds of the '416 patent were superior to Otsuka's prior art compounds.

One of the tests that Otsuka used to prove to the patent office that the '416 compounds were superior was the Mouse Jumping Test.

Dr. Marshall, who is an expert in pharmacology, testified at trial that the Mouse Jumping Test is a test for antischizophrenic activity.

And none of Otsuka's witnesses disagreed with him. In fact, Otsuka's expert, Dr. Nichols, under questioning from the Court, finally admitted that the Mouse Jumping Test in the Nakagawa declaration was a test for antischizophrenic activity.

THE COURT: Basically, I was just asking what else could it be for.

And he said, Well, I guess it's for this.

That's what he said.

MS. HOLLAND: Yes. I have the testimony here, Your Honor.

THE COURT: I know you do.

MS. HOLLAND: The Court asked Dr. Nichols what property Otsuka was trying to demonstrate through the Nakagawa, and he said it was antipsychotic activity, even though Otsuka seems to still be pressing this point in its posttrial papers, given Dr. Nichols' testimony, and given Otsuka's previous admissions that Your Honor heard about during trial, including during prosecution of the '932 patent, when Otsuka told the patent office in no uncertain terms that the Mouse Jumping Test was a test that provides reasonable assurance that a compound has antischizophrenic activity. And the cite for that is DTX-471.

So even though Otsuka is still pressing the point, in light of all these admissions by Otsuka, this really should be a nonissue right now.

Now, as the evidence showed, of the billions of carbostyril derivatives covered by the '416 patent, Otsuka chose only nine compounds to test in the Mouse Jumping Test in the Nakagawa declaration.

In other words, Otsuka looked at the '416 patent and selected the nine compounds that it thought would best demonstrate to the patent office antischizophrenic activity.

And it's undisputed that one of these handful of compounds that Otsuka selected was the unsubstituted butoxy.

As defendants' experts Dr. Press and Dr. Castagnoli testified, the data in the Nakagawa declaration provides what medicinal chemists call a structure-activity relationship, or shorthand, SAR information. It tells a medicinal chemist how a change in structure is going to affect a change in activity.

Now, Otsuka argues that the Nakagawa declaration was not intended as an assay or a study. But that's really beside the point, Your Honor, because the testimony is undisputed that this SAR information does exist in the Nakagawa declaration and would teach the person of ordinary skill in the art how to modify the unsubstituted butoxy.

Can we see closing slide 4, please.

This summarizes the unrebutted testimony about what the person of ordinary skill would understand from the Nakagawa declaration, as testified to by Dr. Press and Dr. Castagnoli.

The Nakagawa declaration teaches the person of ordinary skill exactly what to do to the unsubstituted butoxy in order to increase antischizophrenic activity.

No. 1, it tells the person of ordinary skill in the art to place chlorines at the 2- and 3-positions of the phenyl ring because that increases potency.

It tells the person of ordinary skill not to put a chlorine at the 4-position because that will decrease potency.

It also tells the person of ordinary skill in the art not to change the butoxy linker because butoxy linked compounds are more potent than propoxy linked compounds.

There is no evidence in the record, Your Honor, that rebuts any of these points. They were not directly addressed by Otsuka's experts.

Now, Dr. Press and Dr. Castagnoli also explained why the Nakagawa declaration data about the unsubstituted propoxy would also apply to the unsubstituted butoxy.

The only difference between the unsubstituted propoxy and the unsubstituted butoxy is in the length of the linker. The propoxy has three CH2 or methylene units, and the unsubstituted butoxy has four CH2 or methylene units. This makes the unsubstituted propoxy and unsubstituted butoxy homologs of each other.

And as Dr. Press testified at trial -- and again, Your Honor, this is unrebutted testimony -- the person of ordinary skill would expect homologs to behave in the same way and to have similar properties.

So a medicinal chemist would operate under the assumption that the structure-activity relationship of the propoxy series found in the Nakagawa declaration would apply

equally to the butoxy series.

Dr. Press also explained why the person of ordinary skill would substitute chlorines at both the 2- and 3-positions of the unsubstituted butoxy.

He explained that there's a principle of medicinal chemistry called the additive effect. In other words, each substituent in a molecule makes an independent contribution to biological activity, and these contributions can be combined in an additive way.

So if you know from the Nakagawa declaration that the 2 chlorine substitution improves activity and you know that the 3 chlorine substitution improves activity, the additive effect of this principle of medicinal chemistry tells you that these can be combined to make a molecule with increased antischizophrenic potency.

None of Otsuka's experts disputed this concept of the additive effect, that it's a principle of medicine chemistry, and that it's a principle of drug design.

In this case, the person of ordinary skill would also know from the prior art that Otsuka had actually made a 2,3-dichloro compound. It's undisputed that the 2,3-dichloropropoxy compound was in the prior art. It's in Otsuka's published Swedish patent application SE '945.

Can we see closing slide 5.

The 2,3-dichloropropoxy is Example 134 of SE '945,

and that's DTX-1159T. And the specification of that published patent application states that the compounds of the invention are useful as, among other things, antischizophrenia agents.

So the person of ordinary skill would know that 2,3-dichloro substitution was known and that the compounds were disclosed as having, among other things, antischizophrenic potency.

As I said, Your Honor, Otsuka's experts did not take issue with any of the very specific evidence provided by defendants' experts about the teachings of the Nakagawa declaration.

Otsuka's main strategy for dealing with the Nakagawa declaration is to ask the Court to just completely disregard it because Otsuka claims that it's not prior art. But Otsuka doesn't have a single case to support its position.

Defendants have found three cases that address this issue. In each of those cases the Court found that a document from the file wrapper of an issued patent was prior art and must be considered in the invalidity analysis. And those cases are the Takeda, Bruckelmyer and Bamberger cases which are in our briefs.

There's no question that the contents of a U.S. file wrapper becomes public when the patent issues.

Can we see closing slide 6.

This is the relevancy of our section, Your Honor. It states quite clearly that after a patent issues, the papers in the file wrapper or the file history become public.

Otsuka has tried to distinguish the Bruckelmyer case by arguing that the specification of the '416 patent doesn't contain information that would lead somebody -- an interested person of ordinary skill to search for and locate the '416 file wrapper, but the evidence at trial was to the contrary.

Can we see slide 7.

This is from DTX-6, the '416 patent. As you heard at trial, Your Honor, the patent is entitled "Pharmaceutically Useful Carbostyril Derivatives," clearly teaching the person of ordinary skill that the patent is about carbostyril derivatives. And the specification is a very specific disclosure that the compounds can be used as antischizophrenic agents.

Can we see closing slide 9.

In fact, Otsuka pretty much conceded this point in its reexamination request. This is an excerpt from DTX-121, Otsuka's request for reexamination. And when Otsuka asked the patent office to reexamine the '528 patent, it pointed specifically to the '416 patent as providing a substantial question of patentability.

And Otsuka told the patent office that it could be argued that the use of the compounds of the '416 patent as

antischizophrenia agents is specifically contemplated.

Most of the other arguments that Otsuka makes go to statutory obviousness under Section 103 and not double patenting. For example, Your Honor, Otsuka argues that a person of ordinary skill in the art with the Nakagawa declaration would have chosen the 2-ethoxy compound with the lowest ED50 value as --

THE COURT: No. 44?

MS. HOLLAND: Yes, that's it. Thank you, Your Honor.

THE COURT: I'm not ready for the ten-minute quiz.

MS. HOLLAND: So Otsuka makes an argument that the person of ordinary skill would have chosen this compound 44, the 2-ethoxy compound, as the lead compound, rather than choosing the unsubstituted butoxy.

But that is not an argument relevant to double patenting because as we saw from the Proctor & Gamble case earlier, you can't start the double patenting analysis from any compound in the prior art. It has to be the compound that's claimed in the earlier patent.

And in this case, that compound is the unsubstituted butoxy, Claim 13 of the '416 patent.

THE COURT: So you're saying you're only supposed to look at the unsubstituted butoxy in the prior art for obviousness type double patenting analysis and see how that looks in terms of whether it looked promising toward this

application, namely antischizophrenic. Right?

MS. HOLLAND: Yes, Your Honor. You have to look at the unsubstituted butoxy as compared to aripiprazole. That's the only comparison you can make in the double patenting analysis.

And then the question is, if you look at the unsubstituted butoxy, what does the prior art tell you about what to do with it to increase its antischizophrenic activity?

THE COURT: Even in the first place, you have to look to see whether it looks like it might be antischizophrenic instead of antihistamine or whatever other application. Right?

MS. HOLLAND: Well, I don't think that's correct, Your Honor, because the double patenting jurisprudence from the Federal Circuit says you look at the claims of the prior patent; in this case, the '416 patent.

You start there, and then you say, looking at this unsubstituted butoxy, would it have been obvious to modify it to make aripiprazole?

In this case, when you look at the unsubstituted butoxy, you, first of all, see from the Nakagawa declaration that Otsuka chose it as a paradigm of antischizophrenic activity. It was one of the nine compounds that Otsuka selected to test in the Mouse Jumping Test. So you already

start off with the premise that it has antischizophrenic activity.

The question then is: How do I boost that antischizophrenic activity if I'm the person of ordinary skill in the art? What do I see in the prior art? What does it tell me to do once I have this unsubstituted butoxy?

And the Nakagawa declaration is really quite specific about the changes that need to be made to the unsubstituted butoxy to increase the activity.

THE COURT: Okay. I'm following the argument now. Go ahead.

MS. HOLLAND: Thank you, Your Honor.

THE COURT: But you're looking at that test data right there in the Nakagawa declaration?

MS. HOLLAND: Yes, Your Honor, because that's part of the prior art. So you start with the earlier claim.

And then the question is, a person of ordinary skill with this earlier claim, you know, with the unsubstituted butoxy in their hand, what would they do with it? How would they boost the antischizophrenic activity? What does the prior art tell them to do?

And those teachings are right in the Nakagawa declaration. We're not in a situation here where there's no specific teaching of the prior art, and you just try and kind of, you know, figure out based on a lot of general teachings

what to do. That's not the case here.

We have a specific teaching in this case about what to do with the unsubstituted butoxy in order to boost its antischizophrenic activity.

Otsuka has some other arguments that are also not relevant to double patenting, such as its arguments about secondary considerations, like --

THE COURT: I follow that.

MS. HOLLAND: Okay, Your Honor. Thank you.

THE COURT: In other words, I know what you're going to say. The grand factors you don't look at when you're doing your obviousness type double patenting analysis, according to you. Right?

MS. HOLLAND: Yes, Your Honor, that is what I was going to say.

THE COURT: Okay. Got it.

MS. HOLLAND: So just to sum up on the double patenting point, defendants submit that there was clear and convincing evidence at trial that aripiprazole is an obvious variant of the unsubstituted butoxy, based on all the information in the Nakagawa declaration, and that the asserted claims would, therefore, be invalid for double patenting.

THE COURT: So you don't have to go beyond the Nakagawa declaration to complete your double patenting

argument?

MS. HOLLAND: Correct. That's all you need, Your Honor.

THE COURT: Even though you did pick up the Swedish '945 patent --

MS. HOLLAND: Yes, Your Honor.

THE COURT: -- in your discussion here?

MS. HOLLAND: All you would need was the Nakagawa declaration because that teaches you to make the 2,3-chlorine substitution. The person of ordinary skill in the art would know, because they are medicinal chemists, that there is an additive effect. So of course they would put the 2 -- the chlorines at both the 2- and 3-positions.

THE COURT: Okay. Fine. But are you answering my question?

MS. HOLLAND: Yes. I was --

THE COURT: Nakagawa will do it for you, as you see it, in your double patenting argument?

MS. HOLLAND: Yes. And the SE '945 Swedish application would support that. It would be additional evidence that the person of ordinary skill in the art would make this double substitution, the 2-chlorine and the 3-chlorine, because they would see it in the prior art in the SE '945.

THE COURT: Thank you.

MS. HOLLAND: If the Court -- I'm sorry. Go ahead, Your Honor.

THE COURT: I'll tell you when I'm ready.

Okay. Go ahead.

MS. HOLLAND: Shall I move on to inequitable conduct, Your Honor?

THE COURT: Whatever your outline is.

MS. HOLLAND: As long as the Court has no more questions on --

THE COURT: No, I don't. I was just taking some notes.

MS. HOLLAND: So moving on to inequitable conduct, I just want to say up front that the Federal Circuit is set to hear oral argument in the en banc Therasense case on November 9th.

THE COURT: Can you just spell that, please.

MS. HOLLAND: T-H-E-R-A-S-E-N-S-E.

THE COURT: Go ahead.

MS. HOLLAND: And that en banc argument is on issues related to inequitable conduct.

But there are certain fundamental points about inequitable conduct, Your Honor, that are clear even if the law may shift in some way based on the Federal Circuit's decision in Therasense.

First of all, it's absolutely fundamental that anyone

substantively involved in the prosecution of a patent owes a duty of candor to the patent office, and inequitable conduct is a breach of that duty. It occurs either when somebody with the duty of candor withholds material information from the patent office or makes false or misleading material statements to the patent office with an intent to deceive.

The evidence in this case showed that Dr. Oshiro, Dr. Hirose, and Otsuka's outside counsel, Mr. Van Horn of the Finnegan firm, were all substantively involved in the reexamination prosecution, and they, therefore, all owed a duty of candor to the patent office.

The evidence also shows that they completely disregarded their duty because they needed the patent office to confirm the claims of the '528 patent during reexamination.

THE COURT: So you're saying that the inequitable conduct arises in the reexamination?

MS. HOLLAND: Yes, Your Honor, that's what we're saying.

And I want to focus first on the Hirose declaration.

As Your Honor heard at trial, Otsuka submitted the Hirose declaration to the patent office after everything else had failed. The examiner had already issued a final rejection. The '416 patent, which had been providing patent protection for Otsuka's Abilify product, had already expired.

So unless Otsuka convinced the patent office to confirm the claims, Otsuka was in a position to lose the '528 patent and to lose its monopoly over aripiprazole.

Since all of the arguments that it made to the patent office had failed, Otsuka knew that the only thing it could do at that point was to try to submit a declaration to the examiner that would show or demonstrate that aripiprazole and the other butoxy compounds that were claimed in the '528 patent were unexpectedly superior to the prior art compounds that had the propoxy linker versus the butoxy linker.

And for aripiprazole, it was agreed with the examiner that the closest prior art compound was the 2,3-dichloropropoxy compound because the only difference between aripiprazole and the 2,3-dichloropropoxy is in the length of the linker. Aripiprazole has a butoxy linker, and the 2,3-dichloropropoxy has a propoxy linker.

As Dr. Hirose testified at trial, he was instructed by his superiors to conduct testing that would prove that aripiprazole and the butoxy compounds were superior to the 2,3-dichloropropoxy and the other prior art propoxy compounds. And Dr. Hirose designed his experiments to make sure that the result he got was the result that his employer wanted.

After Dr. Hirose concluded his experiments, Otsuka

put in the Hirose declaration to the patent office, and it represented to the patent office in that declaration that aripiprazole was unexpectedly 23 times more potent than the 2,3-dichloropropoxy compound, and it was more potent in the Anti-Apomorphine Stereotypy Test for antischizophrenic activity.

After the patent office got the Hirose declaration and looked at the results, it decided to confirm the claims of the '528 patent.

Can we see closing slide 10, please.

This is an excerpt from the document that the examiner -- that's in the prosecution history file, which is the examiner's reasons for patentability and confirming the claims of the '528 patent.

As you heard at trial, Your Honor, the examiner confirmed the claims based on the data in the Hirose declaration because, according to that data, the compounds with the butoxy linker, including aripiprazole, were unexpectedly superior to the compounds with the propoxy linker as the 2,3-dichloropropoxy. And again, Your Honor, the examiner came to this conclusion based on the results in the Hirose declaration.

But the evidence at trial showed that Dr. Oshiro withheld information that he knew contradicted what Otsuka told the patent office in the Hirose declaration. He knew

that aripiprazole was not unexpectedly superior to the 2,3-dichloropropoxy, and certainly not 23 times more potent.

The evidence at trial showed that Otsuka had internal data from its own Anti-Apomorphine Stereotypy testing that was done outside the context of trying to get the claims approved in the reexamination that showed that the difference in activity was not 23 times, like what Otsuka told the patent office in the Hirose declaration; it was six times.

Can we see closing slide 11.

This is a demonstrative that was used during Dr. Oshiro's testimony, Your Honor, and it compares the data in the Hirose declaration to what Otsuka knew and Dr. Oshiro knew was the real answer from Otsuka's internal data.

The Hirose declaration told the Court that there was a 23-fold difference between aripiprazole and the 2,3-dichloropropoxy, where Otsuka's internal data showed only a six-fold difference.

Dr. Oshiro could not deny that he was aware of the Otsuka internal data because it was his data. It was actually contained in one of Dr. Oshiro's presentations that he made contemporaneously with his development of aripiprazole at Otsuka.

We also know, based on Dr. Oshiro's testimony, that Dr. Oshiro did not consider a six-fold difference to be anything out of the ordinary, to be unexpected, to be

surprising.

Can we see closing slide 12.

This was from Dr. Oshiro's testimony concerning the six-fold increase in activity that Otsuka saw when it took the propoxy linker in OPC-4392 and made it into a butoxy linker. Dr. Oshiro testified that the difference in activity, which was a six-fold difference, was not a considerable increase and it was not surprising.

The evidence showed that Dr. Oshiro was intimately involved in the prosecution of the reexamination and in the drafting of the Hirose declaration. Dr. Oshiro actually testified at trial that he edited the Hirose declaration.

Dr. Hirose said at trial that Dr. Oshiro attended at least ten meetings with the Finnegan lawyers and with other Otsuka personnel concerning the reexam.

And Otsuka's privilege log, which is also in evidence, shows that Dr. Oshiro had over 300 communications with the Otsuka IP department and with Otsuka's counsel at Finnegan Henderson related to the reexamination.

So Dr. Oshiro clearly knew about Otsuka's internal data that is inconsistent with the Hirose declaration data, and he also knew about the Hirose declaration data because he actually edited and attended meetings where it was discussed.

In addition to withholding the data on the 2,3-dichloropropoxy and aripiprazole, the internal Otsuka

data, Otsuka also withheld the Nakagawa declaration, which, as we saw earlier and which was discussed at trial, would lead the person of ordinary still in the art to expect that a butoxy compound would be more potent than a propoxy compound. In the Nakagawa declaration the unsubstituted butoxy was more potent than the unsubstituted propoxy.

Even if the Court were to believe Dr. Oshiro that he didn't know about the Nakagawa declaration -- which is highly unlikely since Dr. Oshiro was an inventor on the '416 patent and Dr. Nakagawa was also his boss at the time.

But even assuming the Court were to believe Dr. Oshiro, he admitted that he was aware of internal Mouse Jumping data on the unsubstituted butoxy. This Mouse Jumping data was not submitted to the PTO during prosecution of the reexamination.

And Mr. Van Horn, who was Otsuka's attorney at Finnegan, must have known about the Nakagawa declaration because, of course, he prepared the reexamination request. And the reexamination request told the patent office that the '416 patent presented a substantial new question of patentability.

So Mr. Van Horn had to have looked at the '416 patent and the '416 patent file wrapper which contains the Nakagawa declaration. He couldn't have submitted that reexamination request without looking through the '416 patent file wrapper.

This information that was withheld, the information on the 2,3-dichloropropoxy and the unsubstituted butoxy, are highly material in this case because they directly contradict the one essential single argument that Otsuka made to overcome the patent office's rejection: That a change from a propoxy linker to a butoxy linker showed unexpected superiority in antipsychotic activity.

The internal Otsuka data and the Nakagawa declaration data both show that any increase would be expected, not unexpected.

Dr. Oshiro was on the stand, Your Honor, and he never explained why the inconsistent data wasn't disclosed to the patent office.

And Mr. Van Horn never even showed up at trial. He was on Otsuka's witness list, but Otsuka decided not to call him to the stand. And we submit, Your Honor, that the Court should be able to infer from that that his testimony would not have been helpful to Otsuka.

Not only did Dr. Oshiro and Mr. Van Horn withhold information about the 2,3-dichloropropoxy and the unsubstituted butoxy; the Hirose declaration actually has a false statement in it, or at the very, very least, a misleading statement.

Can we see closing slide 13.

Closing slide 13 has an excerpt from the Hirose

declaration, which is DTX-399. This is a statement that was discussed at trial at length. Otsuka told the patent office that the observation for stereotyped behavior will be performed by an observer blind to the treatment received by the mice.

A reasonable examiner would have understood that statement to mean that only one observer scored the stereotyped behavior, and that that one observer did not know which drug the mouse had been given at the time he was observing the stereotyped behavior.

But the raw data and the testimony at trial demonstrated, and this is undisputed, Your Honor, that there were not one observer. There were two observers, Dr. Hirose and Dr. Kikuchi, and that they were not blind to the treatment. They knew exactly what drug had been given to the mouse that they were observing and, of course, they also knew the purpose of the test. They knew that they needed to show that aripiprazole was more potent than the 2,3-dichloropropoxy.

So why is this false statement important?

Can we see closing slide 14.

As Dr. Beninger testified at trial, the data in the Hirose declaration can't be meaningfully interpreted because of the confound and bias. The confound, as Dr. Beninger testified, results from the fact that there were two

observers rather than one observer. And the bias comes from the fact that the observers knew exactly what drug the mouse had been given. And they could, therefore, bias their results to show that aripiprazole was more potent than the 2,3-dichloropropoxy.

Now, what did Dr. Roth, Otsuka's expert, say about this?

We know, Your Honor, it's undisputed that Otsuka could have designed the experiment to have one observer rather than two observers, and that the observers could have been blinded to the treatment, and those all would have improved the test.

What did Dr. Roth, Otsuka's expert, say? To him, the design of the Hirose declaration experiments was marvelous. He said it was a marvelous way to do the experiment. He had no problems with it at all.

And Your Honor, we think this is just one example of Dr. Roth providing testimony at trial that was simply not credible.

Now, a reasonable examiner would have, of course, considered it important to know what Dr. Hirose actually did rather than what the declaration says he did, which is not accurate, because the examiner needed to be able to assess whether or not the results of the Hirose declaration were reliable. Otsuka didn't give the examiner enough information

to be able to make that assessment.

Can we see closing slide 15.

Dr. Beninger testified at trial that the information about the conduct of the experiment is critical to understanding and judging and evaluating the data. And the patent office simply did not have accurate information about the conduct of the experiment.

The false statement in the declaration was, therefore, highly material. If the PTO had known about this potential for confounding and bias, it wouldn't have relied on Dr. Hirose's results, for all the reasons that Dr. Beninger gave at trial about the confound and bias.

In addition to all the problems with the Hirose declaration, Otsuka made other false and misleading statements during the reexam.

The examiner repeatedly rejected all the claims of the '528 patent. There were five, what the examiner called exemplary prior art carbostyril derivatives. One of those, it's undisputed, was the unsubstituted butoxy.

How did Otsuka respond to the examiner's rejection?

Can we see closing slide 16, please.

Otsuka made an affirmative statement to the patent office that there is no evidence that the five exemplary carbostyril derivatives -- and the evidence showed, Your Honor, and it's undisputed that one of those was the

unsubstituted butoxy -- have the property of treating schizophrenia. That's a statement that Otsuka made during prosecution, and that statement is false.

As the evidence at trial showed, the prior art Nakagawa declaration provided data confirming that the unsubstituted butoxy had good antischizophrenic activity. It was actually one of the compounds that Otsuka itself chose as an exemplary compound to demonstrate antischizophrenic activity.

So Otsuka's statement that the unsubstituted butoxy did not have the property of treating schizophrenia was false.

THE COURT: I know we have a transcript, but since we're going to hear argument back and forth today, just taking these few notes helps me.

MS. HOLLAND: Yes, Your Honor. Shall I continue?

THE COURT: You may now. Thank you.

MS. HOLLAND: I want to spend a moment talking about intent to deceive. As the Court is no doubt aware, it's very rare for someone to get up on the witness stand and admit that they intended to deceive somebody. Federal Circuit law recognizes this, and it doesn't require direct evidence of intent.

Can we see closing slide 17.

This is from the Federal Circuit's decision in the

Bruno case. What the Federal Circuit said was that intent to deceive is generally inferred when there is no credible explanation, because normally you would expect somebody, if they were innocent, to get up on the stand and try to present some kind of reason for its action or inaction.

In this case, the record shows a pattern of misleading information to the PTO and withholding of material information from the PTO in order to get the '528 patent claims confirmed in the reexam, no matter what had to be said or what had to be done to get that accomplished.

Astonishingly, Otsuka did not make any attempt at trial to explain its actions.

Dr. Oshiro was on the stand. He never explained why he didn't submit the internal data on the 2,3-dichloropropoxy. He never explained why he didn't submit the internal data on the unsubstituted butoxy.

And Mr. Van Horn never even testified, so of course he didn't offer an explanation for why he didn't disclose the Nakagawa declaration during the reexamination.

The only reasonable inference here is that Dr. Oshiro, Mr. Van Horn and Dr. Hirose intended to deceive the PTO.

And defendants submit that the evidence established by clear and convincing evidence that the '528 patent is unenforceable for inequitable conduct.

THE COURT: Thank you, Ms. Holland.

Would we like to take a five-minute break before we get into obviousness?

(Recess taken.)

THE COURT: Okay. Mr. Feldman.

MR. FELDMAN: Good morning, Your Honor. I'm Steven Feldman on behalf of the Apotex defendants.

Your Honor, I'm going to talk to you this morning about obviousness. I have this outline here and whatnot, but I think it might make more sense for me just to sort of get to the issues that I think are most important right now.

THE COURT: As you wish. However you want to do it.

MR. FELDMAN: You know, one issue -- and I'd like to really get to this -- is the issue of lead compound because it's come up in the briefing. And I just want to explain it to the Court and give you our views on it and where the evidence is on the compound.

Lead compound is really just about justifying your starting place, Your Honor. And I think that we have justified our various starting places.

THE COURT: Three starting places?

MR. FELDMAN: Yes.

THE COURT: Okay. Let's get them down. You have the unsubstituted butoxy. Right?

MR. FELDMAN: Correct. You have OPC-4392. And you

have the propoxydichloro compound.

And then generally, the rest of the analysis is about explaining, showing your work, connecting the dots; in other words, explaining how you get from the starting place to the claimed compound.

And I think that our evidence in this case is very strong in that respect because it really follows the teachings of the art.

Some of the cases that the defendants rely on, there's problems with the starting place. There was no reason to start there. It was taught in the art that that was a bad place to start. There were specific teachings really negating it.

And then there's other problems in the cases that they cite. And the cases I'm talking about are like the Daiichi case and the Takeda case and the Lilly case. And the problems in those cases were that in the way that they tried to connect the starting place to where they eventually got, the art didn't really teach them to do that, either.

And so those cases really were problematic and could be criticized with respect to hindsight and trying to sort of justify the compound that you ultimately reached by starting there.

That's not our case, Your Honor. I think if we fairly treat the prior art, particularly the teachings of the

Nakagawa declaration, the teachings concerning the OPC-4392 contain, for example, the Murasaki '87 article, the teachings of the Wise poster, and the other teachings.

And I think what we have here is a real direction, real pointers to make the types of changes that we're talking about to get to the compound aripiprazole and the other similar compounds that Dr. Castagnoli talked about, having methyl and chloro substituents and chloro-chloro substituents at the 2,3 positions on the phenyl ring.

Your Honor, this is also sort of a special case, compared to some of the cases the defendants cite, although not all of them, in that it's a genus species case.

When you have a genus species case, the reason that someone is able to claim a genus is that there's some commonality between all the compounds claimed therein. If there's not that sort of commonality in properties, you cannot claim the genus. You're not allowed to claim the genus.

So for Otsuka to have claimed the genus -- and they describe the sorts of activities that these compounds were expected to have. And I'm talking about now the '416 patent. And in the specification of that patent, they described in detail the types of activities that these sorts of carbostyril derivative compounds would be expected to have.

And what were those properties? Those properties

included antischizophrenic behavior. There was testing that was described in the specification. Those are antipsychotic and antischizophrenic testing. Those were the types of testing that Otsuka itself had used to identify antipsychotic agents.

So for Otsuka to come in here and tell the Court that, no, you would never think that anything in the '416 patent was anything but an antihistamine, I think it's contrary to what's stated in that patent, what they told the patent office, and what they really tried to do here, which was block off that whole area of carbostyrils from competition in both the antihistamine, but also the antischizophrenic area.

Your Honor, when there's a genus species situation, and now you're going to try to claim a specific species from within the genus, it's not enough just to claim a particular species. There's got to be something special about that particular species that then distinguishes it over and above what's already claimed in the genus.

And I think if we go to where the patent office was in examining these compounds --

And Darren, if you could pull up DTX-121, pages 1322 to 23.

I think we'll see that the patent office was sort of in the same place that we are. It's talking about the

'416 patent, the DE '105 patent, and it says the teachings are very clear in the prior art.

And it talks about the fact that you have this genus. The priority has exemplified a fair amount of compounds to cover the scope of the genus, the motivation and teachings within the scope of the prior art. It is inherent to the scope of disclosure with a reasonable expectation of success.

It is not a question of picking and choosing among several variables. It is just making other species of the taught genus. That's where the patent office was.

THE COURT: What's your citation, for the record?

MR. FELDMAN: Sure. It is DTX-121, and the pages are 1322 to 1323. We had numbered it at the bottom.

THE COURT: Thank you.

MR. FELDMAN: Okay. So the reason that Otsuka then had to come back to the patent office -- and again, this was a final rejection -- the patent office wasn't buying them just claiming the particular species of aripiprazole was enough.

So they had to come back to the patent office, and what they had to do was they had to show some unexpected superiority of this particular compound.

And that's why they bothered to do the Hirose declaration, why they bothered to do this testing. They had to try to prove that there was something special about

aripiprazole over the prior art.

And Otsuka -- and the patent office agreed that the closest prior art was the propoxy dichloro compound. Otsuka complains now that that's the starting place. Well, that's the starting place that they agreed with the patent office was a logical starting place, and it was the closest prior art. So I think it's a logical starting place here as well.

What they represented to the patent office was that that propoxy dichloro compound wasn't nearly as good in the Stereotypy Test, in terms of potency, as a butoxy homolog of that particular compound, which was aripiprazole. And that's the representation that they made.

And the premise that they had is going from a propoxy linked compound to a butoxy linked compound. Okay. The butoxy linked compound would be unexpectedly better. Okay. That's why they ran these tests. They were trying to prove this unexpected better-ness. Okay.

But the problem is, you're in 2005, and they knew what they needed to show. They had to show that this particular compound was not just a little bit better because I think the examiner would have found, and I think, as Otsuka's witnesses and Otsuka itself has said, you know, just a little bit of better isn't enough to distinguish the other compounds. So you needed a lot of better. Okay.

So when we get into the compound and the bias and

knowing what you're trying to test for, as opposed to just sort of interpreting scientific results and knowing what you're trying to do to show this unexpected better-ness, that's why 23 times is significant.

Well, what's also significant, Your Honor, is the fact that in 1987 they already had stereotypy data, okay, and it didn't say 23 times better. It said six times better. And as we've heard, six times really isn't all that significant, it's not all that much better, and it wouldn't have been enough for the examiner, either, in terms of allowing this particular patent.

That's why it's so significant in terms of the Hirose declaration. That's why it's so significant that the way it was tested wasn't as clean as it should have been. And the fact is they weren't really interpreting test results. They were trying to create test results to prove a point to the patent office. That's not really science, Your Honor.

In terms of the expectations --

THE COURT: Okay. Go ahead.

MR. FELDMAN: In terms of the expectations, in terms of what was taught in the art or expected in the art in going from a propoxy linked compound to a butoxy linked compound, I think the Nakagawa declaration and the Wise poster fairly clearly taught that making that change, extending the linker link, was going to have an impact on potency that was going

to increase the potency. So I think the expectation going in is that it is going to increase the potency.

As Ms. Holland said and explained from the evidence, Otsuka had to have known about the Nakagawa declaration. It was its own declaration.

And if you look at the Haruki memo and some of these other things, clearly Otsuka was paying attention to what Parke-Davis was doing on these things. Too. And the data was all there to be seen.

So for Otsuka then to come in and say that this is unexpected that you're going to get an increase in potency, I think the evidence really belies that. So that can't be what's special about aripiprazole in this case. The increase in potency from going from a propoxy linked compound to a butoxy linked compound was expected.

Now, Ms. Holland talked a little bit about the Mouse Jumping Test and why that was a known antipsychotic test and a schizophrenic determining test. There was the Lal paper. Dr. Marshall testified at length. We covered it a lot in our briefs.

And of course, most importantly, I think, is Mr. Irving's statement in the prosecution of the '932 patent, where now Otsuka is trying to get a patent on this stuff, relying on the Mouse Jumping Test, and they tell the patent office that, yes, mouse jumping is what you use to show an

antischizophrenic agent. Everybody knows that.

So I think Otsuka is really stuck with that statement, and they're stuck with the Mouse Jumping Test as showing antipsychotic potency.

And I think, as the testimony showed, it does ultimately talk about dopamine blocking, the dopamine hypothesis, this theory that I think everybody agreed was sort of the prevailing theory at the time in terms of what people were trying to do. I think the Mouse Jumping Test lines up very well with that.

And as Dr. Marshall also testified, you can correlate the Mouse Jumping results to the Stereotypy results with respect to a lot of the prior art known antischizophrenic agents.

Now, Otsuka attacks the Wise poster in a couple of ways. One is evidentiary.

THE COURT: So you're saying Mouse Jumping pertains to showing a potential for antipsychotic effect, and it pertains to probably blocking the D2 postsynaptic receptor?

MR. FELDMAN: Yes, Your Honor.

THE COURT: Both?

MR. FELDMAN: Yes.

If I can just talk briefly about the Wise poster. We've covered in our briefs why it is prior art. The fact is it was actually dated. Dr. Wise testified in his deposition,

I think, credibly explaining. He remembered the conference. He remembered making the poster. He remembered passing out the poster.

There's really no contrary evidence. There's nothing showing that there's something to refute Dr. Wise's testimony and the fact that the Wise poster is, in fact, prior art.

And as you'll recall from the MIT case and some of the other cases that we've cited, the fact of it being available to the public, at this public display, and the fact that it was passed out to members of the public is enough to make it a 102(b) prior art printed publication.

Now, Otsuka also challenges the Wise poster on the grounds that it's not a carbostyril; it's a coumarin. And I think we went on at length at trial explaining that it's really a small difference.

Structurally, it's very similar in terms of the way the compound lines up. It's the difference between an NH group on the ring or an oxygen. Okay. And those are called isosteres. And the testimony at trial showed that people would expect isosteres to behave, in most respects, very similarly. And I think that the evidence, in fact, shows that that's what happened.

The way that these particular compounds lined up with respect to the linker link, with respect to the linker attachment, with respect to substitutions on the phenyl ring,

all lined up quite nicely, I think.

And don't forget that when Otsuka was prosecuting the '416 patent, they had their own expert in an interference proceeding where Otsuka's lawyers, again from Finnegan, were taking the testimony of their own witness because that's how you do it in an interference proceeding. And he said that coumarins and carbostyrils were very structurally similar.

You know, it was interesting, too, during the trial when Dr. Wise was talking about the clozapine derivatives, he gave an example of clozapine as opposed to asenapine.

THE COURT: Dr. Wise?

MR. FELDMAN: I'm sorry, Your Honor. Dr. Nichols. I'm sorry.

He was talking about the clozapine and the asenapine compounds, and he said those are fairly structurally similar to him, even though there are a lot of different structures there. And he said really the main difference, and they were isosteres, was again this NH group on the clozapine as opposed to this oxygen group on asenapine.

So when he's talking about clozapine derivatives, they're similar; but now when he's trying to distinguish isosteres of carbostyrils, like the coumarin, suddenly there's a great difference here. I think that goes to the credibility of what they're saying on this.

So now, if I can, I'd like to talk a little bit just

about justifying the starting place for both the unsubstituted butoxy and also OPC-4392.

Ms. Holland went into some length in terms of the modifications to the unsubstituted butoxy compound. But the reason why you would start there, in addition to it being specifically exemplified in the Nakagawa declaration, specifically claimed in the '416 patent, is that it really embodied sort of the logical starting place. As Dr. Press put it, it was a perfect platform to start from.

Once you draw the inference, which I think the prior art taught, that a butoxy template was where you wanted to go to improve the potency of the carbostyril compounds, it makes perfect sense to start with this unsubstituted butoxy compound, and then make the sorts of substitutions that we're talking about.

You would still take into account the teachings of the other art, including OPC-4392 and Nakagawa, about the types of substitutions that you might want to put on the phenyl ring and where you might want to put them, for example, at the 2,3 position.

But really, what you had in the Nakagawa declaration and this unsubstituted butoxy compound was sort of a reason to make sort of the next generation starting place beyond the propoxy compounds.

You've drawn the inference that growing a propoxy

linker is going to improve the activity, but you already know there's some benefits to having the other types of compounds, like the OPC-4392, and its benefits in humans in terms of treating negative symptoms, in terms of good toxicity profile, in terms of low EPS. You try to keep close to that, but still make the types of changes that you want to make to enhance the potency.

Now, OPC-4392 is another, I think, logical starting place. OPC-4392 was, as the evidence showed, the one carbostyril compound that had been tested in humans.

Now, the dispute at the trial was whether this was a success or a failure. But I think if you fairly read Otsuka's own reports and reports of its scientists at the time, I think that they were not treating OPC-4392 as a failure. They weren't touting it as a failure in the art. And I think people in the art wouldn't have viewed it as a failure.

Can we go to ADX-28 that we used before.

In terms of the properties or the wish list of an antipsychotic agent, Dr. Castagnoli and others explained that what you really want to do is you want to be able to treat the positive symptoms, treat the negative symptoms, have a nontoxic compound, and have a good side effect profile.

The evidence showed that OPC-4392 --

THE COURT: What are you citing from; today's slide?

MR. FELDMAN: Today's slide, although there's also testimony cited --

THE COURT: Oh, sure.

MR. FELDMAN: -- in the briefs.

THE COURT: But -- yes.

MR. FELDMAN: But right now I'm talking about ADX-28.

THE COURT: What is ADX?

MR. FELDMAN: That was a demonstrative we'd used at trial.

THE COURT: Okay. It's already --

MR. FELDMAN: Already --

THE COURT: -- a demonstrative at trial?

MR. FELDMAN: Yes.

THE COURT: That's fine.

MR. FELDMAN: Okay. I'm sorry.

THE COURT: ADX-28?

MR. FELDMAN: Right.

And the underlying basis for a lot of this is the Murasaki 1987 article, which was DTX-388T, and also the Gerbaldo abstract, which is DTX-990.

And the other point that I should add is that OPC-4392 was, in fact, Otsuka's starting place for developing aripiprazole. If you look at Dr. Murasaki's 2006 article, he says that it all started from OPC-4392.

There was also testimony from Dr. Oshiro in a

presentation that he had given where he says that OPC-4392 is the origin of the development of aripiprazole, although I should say that there was a dispute during trial about the translation as to whether it was the cause or the origin, a dispute over a Japanese word there.

But I think, given what the actual evidence is and even Otsuka's internal data that we'll get into a little bit later, that OPC-4392 was foremost in terms of the development of aripiprazole.

THE COURT: It was first. Right?

MR. FELDMAN: Right.

Now, in terms of OPC-4392, again, as I mentioned, it was almost there. The issue of not strong was another issue that came up at trial and what that meant.

Otsuka took the position that what that meant is that it had no activity in terms of treating positive symptoms.

Our view was that if that was what had happened, that the contemporaneous articles at the time would have said it had no activity in treating positive symptoms.

But that's not what those articles said. They said not strong. In other internal Otsuka materials, they said it was weak. And again, we talked about there was a Gerbaldo paper that came out just a month too late to be prior art, but it talked about actually treating --

THE COURT: What's the author's name?

MR. FELDMAN: Gerbaldo.

And it talked about treating hallucinations, which everyone agrees, I think, is a positive symptom of schizophrenia, in four out of four patients.

Now, Dr. Roth, when he talked about the Gerbaldo article, obviously said there was some negativity as well there. But the fact remains it seemed to be having some impact on these people, good or bad. And you can't ignore the good.

The law, in fact, says that you take the reference fairly for what it teaches. And the fact that it had some showing of the good is sufficient really to show that there's a basis for starting with it. That's the Medichem case that we cite in our reply brief.

The other thing about the not strong is that it provided a natural sort of impetus, a natural reason, a natural motivation for improving this compound.

In other words, our concept is that -- and the concept, I think, that people in the prior art would have had, and I think the evidence showed that, was that you would want to improve this compound. You're not going to throw it away.

The compound was treating negative symptoms. The testimony was that treating negative symptoms was sort of special here; that other compounds, particularly the typical

antipsychotic agents, never treated the negative symptoms.

Having a good side effect profile was, again, a very promising thing. The typical antipsychotic agents had serious side effects like EPS and hyperlactemia.

And so these were some real notable features of OPC-4392.

So then the question becomes, okay. Well, it's not strong at treating the positive symptoms. What do we do? How do we make it better?

Well, the prior art taught how to make it better in terms of improving potency. And that's really where the obviousness case comes in in terms of the motivation to make the types of changes that we're talking about, the motivation with respect to OPC-4392 to grow the linker length, to switch the methyls to chlorines.

And the particular prior art that we're looking at here, the Nakagawa declaration, taught the benefits of a butoxy over a propoxy linked compound in terms of increasing potency. The Nakagawa declaration taught the benefits of potency with respect to chlorines at the 2- and the 3-position.

THE COURT: Are you still at Nakagawa?

MR. FELDMAN: Still at Nakagawa.

The Wise poster also taught the benefits of the butoxy linked compounds in terms of increasing the potency,

so that's a thing to do.

The Wise poster also contained data showing that a chlorine at the 3-position was going to be more potent than a methyl at the 3-position. So that's another impetus to try these chlorines at the 2- and the 3-position on the phenyl ring and potentially swap them out with the methyls.

And when Dr. Castagnoli created his group of eight compounds, that's exactly what he did in terms of trying the methylmethyl, the methylchloro, the chloromethyl, and the chloro plural compounds. So he did systematic changes --

THE COURT: Dr. Castagnoli?

MR. FELDMAN: Yes, Dr. Castagnoli, yes.

THE COURT: Just wanted to make sure.

MR. FELDMAN: In terms of explaining what he thought a person of ordinary skill in the art would do.

THE COURT: All right. Yes. He didn't actually do it. He described it.

MR. FELDMAN: He described it. Sorry.

In fact, he said that he thought that a person of ordinary skill in the art would be negligent if they didn't make these types of changes because, again, you had the teachings. You had the target. You knew that you needed to increase the positive symptom efficacy. And you had ways. He had tools in his tool chest on how to do it.

The other thing that I wanted to mention is

homologation. That became important at the trial in terms of the systematic types of changes that a medicinal chemist might make.

And there are some cases that I believe that Otsuka cites where homologation is just all that someone has, and so they'll say, Okay. Well, it would be obvious just to make a homolog.

We have much more than that here. As you'll recall from the Burger article that was put up on the board with Dr. Castagnoli, medicinal chemists view homologs as very special compounds. In the homologous series they expect that there's going to be a parabolic increase in terms of the potency. And finding the peak in terms of potency is often what you're looking for.

And I think that the Nakagawa declaration and also -- and even to a greater extent, the Wise poster -- the Wise poster went from the ethoxy to the propoxy to the butoxy to the pentoxy, so they really did the entire series. And what they found was that the butoxys were the most potent within that series. That's just another motivation to go to butoxy.

Now, Otsuka also spent some time talking about, well, based on the Nakagawa declaration, the 5-position compound with the linker was the most potent, so someone with ordinary skill in the art would start there.

We have two main points on that. One is, even if it

would have been obvious for someone to start with the 5-position linker and make changes, that's fine, but it doesn't make the 7-position linked compounds less obvious. There were still lots of teachings with respect to the 7-position compounds.

And in fact, there was lots more data on 7-position linked compounds than what was in the Nakagawa declaration. Prominently, OPC-4392, which had been a 7-linked compound, you had the compounds of the Wise poster, which taught that 7-position was, in fact, the place to put the linker.

So you had more data. You had more information about it, which would have led someone, I think, to stay closer to the 7-linked compound. That's what Dr. Castagnoli testified.

The other testimony was that changing the linker position was a big structural change. And so as Dr. Castagnoli and Dr. Press testified, at least initially when they were trying to improve the potency, they wanted to stay close to what's sort of known and been fairly successful so far and stick with that template and make the smaller changes, such as growing the linker or playing with the substituents on the phenyl group. When you change the position, now you're changing the real relationship amongst all the molecules.

But even if the 5-position option was added, Dr. Castagnoli testified that the total number of obvious

compounds would only go from eight to 16, in his opinion.

And so, you know, even if we take into account the 5-position compounds, but still take into account all the other teachings of the prior art, you're not dealing with a particularly large universe of compounds.

And we can contrast that to the Merck v. Biobel (phonetic) case, where there were 1,200 compounds, all of which were determined to be obvious.

And just to drive this point home, the way the art was, it almost didn't matter where you started. There were certain characteristics that were taught by the prior art that a compound, in terms of optimizing potency, you were going to want to have.

And also, not just optimizing potency, but also keeping the benefits of the other compound, the OPC-4392 compound, in terms of treating negative symptoms, a good side effect profile, low toxicity.

And in fact, Otsuka's journey to aripiprazole wasn't much of a journey at all. It was a matter of a couple of months. There was no "a-ha" moment.

All that Dr. Oshiro did in terms of arriving at aripiprazole was making the same sorts of routine changes, the same sorts of medicinal chemistry studies, that were proven out by the Wise poster and even what was shown in the Nakagawa declaration.

In other words, what did he actually do? He screened the compounds that he had already had made to see which was sort of the most promising, the most potent in the Stereotypy Test.

And then what did he do? He studied the effects of the linker length and the linker position and the substituents on the phenyl ring, just like they do in the Wise poster.

So I think that's diagnostic proof, I think, that what he was doing was, in fact, ordinary, not extraordinary.

And I'd like to touch on, Your Honor, you know, the KSR case from the Supreme Court, which is our most recent direction from them. It says that the results of ordinary innovation are not the subject of exclusive rights under the patent laws. So there was some degree of innovation, some degree of routine experimentation, that does not qualify for a patent.

And our position, and I think the evidence showed, is that what Otsuka did here does, in fact, fall within that ordinary innovation level and is not extraordinary and is not meriting a patent, particularly a second patent that's going to extend their ability to exclude people from the carbostyril space for another ten years.

THE COURT: From when it was issued?

MR. FELDMAN: Well, for another ten years from when

the '416 patent expired.

Otsuka spent some time talking about the clozapine and the risperidone as other possible starting places. And as a general matter, maybe those could have been starting places for someone's antischizophrenic drug discovery program.

But what the statute says, 35 USC 103, on obviousness is that you compare the compound that's being claimed to the prior art, and you compare the differences, and you make an ultimate determination as to whether the differences between the compound and the prior art make that compound patentable.

And you don't get to exclude some of the prior art. You have to deal with all the prior art, and all the prior art included the carbostyril derivative compounds.

And as we expressed, there were obviously reasons to start with the compounds that we started with. So the fact that you would have started maybe with a clozapine or risperidone-derived compound, you know, in some other research program doesn't really prove anything.

And we cite some cases to that effect that just, again, because one path might be obvious doesn't make other obvious paths less obvious.

Now, one other issue that I wanted to deal with had to do with the secondary considerations. And where the secondary considerations fall is in the ultimate obviousness

analysis, which ultimately is a legal conclusion.

What you're doing is you're weighing the evidence of obviousness and the evidence of nonobviousness. Then you're making an ultimate legal conclusion as to whether this particular claimed invention is worthy of a patent.

What's significant here is the fact that the aripiprazole compound was already covered by another patent. And I'm not sure if that ultimately came through clearly at trial in terms of the significance of that with respect to commercial success and whatnot.

But the idea was that, you know, there's an inference that needs to be drawn from these secondary considerations. Okay.

It's not enough just to say, "Oh, we sold a lot of this drug" or "Oh, they copied it" or "Oh, you know, it got some awards" or something like that. Okay. That's not enough to prove nonobviousness. For that type of evidence to establish nonobviousness, it has to support an inference of nonobviousness.

What -- the inference that we're talking about is often that, well, yeah, if someone knew that this was going to be a commercial success, or if it was so obvious that you knew you could make this and sell a lot of it and make a lot of money, then anyone would have done it. Okay. And the fact that no one did it means that it's not obvious.

That's really the type of inference that people are seeking to draw when they're using commercial success and other of those factors as an indicia of nonobviousness.

What we have here, though, is that no one could play in this carbostyril space. You know, Otsuka put barbed wire around their sandbox here. The carbostyril sandbox was blocked. No one could play there. No one had an economic motivation to play there because they knew that even if they made the greatest carbostyril compound in the world, okay, they couldn't bring it to market.

THE COURT: I understand that.

MR. FELDMAN: Okay. You know, the same -- that same theory underlies all the other indicia as well. Without -- with some other explanation as to why people either wouldn't have done aripiprazole, being this other patent, then these other indicia also fall.

And with respect to copying, I think, as we've briefed, you know, copying in an ANDA case is really sort of not indicative of anything since the statute basically requires generic drug manufacturers to make the same compound if they want to compete. And the statute encourages them to try to do that.

THE COURT: Okay.

MR. FELDMAN: That's all I have, Your Honor.

THE COURT: Thank you.

MR. FELDMAN: Thank you.

THE COURT: Anyone else on behalf of defendants before we turn to the plaintiff?

MS. HOLLAND: No, Your Honor.

THE COURT: Okay. You can have your time to reply.

MS. HOLLAND: Thank you.

THE COURT: Mr. Monroe, would you like to proceed or take a little break?

MR. MONROE: A short break would be very helpful.

THE COURT: That's fine.

MR. MONROE: Thank you.

(Recess taken.)

THE COURT: Thank you, everyone.

Counsel.

MR. MONROE: Good morning, Your Honor.

As I noted at the start of this trial, the issues in this case are not as simple as the defendants argue, and their cookbook theory of obviousness is based on nothing but hindsight.

And it doesn't reflect the complexities of antipsychotic research, as shown at trial, and the vigorous effort which ultimately led to aripiprazole, nor does it do justice to one of the most challenging areas in drug discovery research.

And I think it's important for us to focus again on

some of the background and the state of the art at the time of the invention to put context to the obviousness inquiry and even the nonstatutory obviousness type double patenting theory.

As we had discussed at trial, there was a lot of research which led to lots of failures, and Otsuka was also one of those failures. Fortunately, Dr. Oshiro went back to the drawing board following such a failure within his own company, and the end result is that doctors and patients now have a very unique compound that they did not have before to treat one of the worst mental illnesses.

I noted during my opening statement several things which we intended to prove at trial, and I think our posttrial submission shows that we accomplished that goal.

I would like to focus today on what the defendants did not prove because that is the issue here. They have the burden of proof. They have the burden of establishing by clear and convincing evidence that each of the asserted claims is unpatentable, obvious over the prior art, or that the patent itself is unenforceable. And they have failed to meet this burden.

I will discuss in detail the flaws in their argument, but would first like to address an overarching flaw in their entire analysis. And the most important is they failed to address the Federal Circuit case law which governs this sort

of case involving a pharmaceutical compound claim.

If we could have that first slide, PD-9101, on the screen.

As the Federal Circuit recently stated, again, in the Daiichi case, the party asserting obviousness of a claim to a pharmaceutical compound must first identify a lead compound in the prior art that one of ordinary skill in the art would have chosen over other compounds in the prior art.

Defendants have not even attempted to make such a showing that one of ordinary skill in the art would have chosen one of their compounds over the other compounds in the prior art.

THE COURT: Compound or compounds?

MR. MONROE: Correct, Your Honor. Over other prior art compounds.

THE COURT: No. I'm saying select a proposed lead compound or compounds --

MR. MONROE: Compounds.

THE COURT: -- over other compounds?

MR. MONROE: Correct.

And if we could turn to the second slide, PD-902.

And as the slide PD-902 shows, the defendants have failed to prove that one of ordinary skill would have selected their proposed lead compounds over the numerous other, more promising compounds in the art, including the

clozapine-like compounds, the risperidone-like compounds, and other carbostyril compounds, to the extent those were actually relevant to an analysis of picking a lead compound for antipsychotic research.

They have not shown why the lead compounds they have chosen or even carbostyril compounds in general would have been chosen over these other promising lead compounds, such as clozapine-like and risperidone-like compounds.

Instead, they used hindsight and looked only to structurally similar carbostyril compounds as the lead compound. This is an approach the Daiichi Corp. said runs contrary to the Federal Circuit case law.

As shown by PD-903 on the screen, the Federal Circuit specifically noted that it's contrary to the case law to rely simply on the closest prior art as being dispositive of the lead compound issue.

Therefore, defendants' obviousness theory fails at the very first step of their analysis because they have not shown that their lead compounds would be chosen over the other compounds in the prior art in the subject matter area.

The defendants' obviousness theories are further fundamentally flawed in that they were presented through experts who lacked the sort of expertise necessary to render this analysis or even interpret the very documents they relied upon.

For example, Dr. Press relied heavily on certain papers concerning OPC-4392, including the 1987 Murasaki reference. He candidly admitted that he did not understand the statement in this paper concerning the "activating agent" of OPC-4392. He had no understanding that this indicated a potentially dangerous side effect associated with 4392.

He similarly demonstrated a lack of understanding of the key details of the documents upon which he relied. He made repeated mistakes in his testimony concerning the experimental data disclosed in the Wise poster; for example, incorrectly opining that the LMA Test is a test for D2 antagonism. He was unaware that this is a nonspecific test associated with false positives.

And this was Dr. Castagnoli I jumped to, Your Honor. I'm sorry. Dr. Press was the one who did not understand what activated the action, and Dr. Castagnoli is the one who could not testify appropriately on a lot of the pharmacological tests and what they meant.

And all of this is laid out also in our posttrial submissions to identify the lack of expertise with respect to interpreting particular documents at trial.

And defendants have made no efforts to defend their mischaracterizations or inaccurate understandings of the prior art in their papers. Multiple -- these multiple flaws are fatal to defendants' position.

And I would like to now discuss in further detail the evidence at trial which overwhelmingly demonstrates the nonobviousness of the invention. I'm going to begin with the obviousness issue, and then address double patenting and inequitable conduct.

THE COURT: Okay. Fine.

MR. MONROE: It is without dispute that the first place you start in an obviousness analysis is the patent claims. And in this case Otsuka is asserting three claims, as we showed at court.

And just for recollection, I'd like to show slide PD-904.

This shows the three claims. One, to the chemical structure of aripiprazole, is Claim 12. The second, Claim 17, is the pharmaceutical composition of that drug for treating schizophrenia. And 23 is a method of treating schizophrenia wherein the carbostyril compound is aripiprazole.

THE COURT: Actually, 23 was added in the reexamination.

MR. MONROE: That's correct, Your Honor. The patent office allowed Otsuka to add additional claims after the patent office had reviewed the prior art and determined the patentability of aripiprazole, and also the patentability of using that unique compound to treat schizophrenia.

The reason I wanted to point out the three claims --

THE COURT: And actually, it had already gotten FDA approval.

MR. MONROE: That is correct. And the patent office was simply confirming that that product was -- that discovery was patentable, for which we had FDA approval.

I wanted to point out the three claims because in the posttrial submissions the defendants grouped those claims as if they stand or fall together. And if Claim 1 is invalid, then Claim 17 and Claim 23 fall.

And that's incorrect. The Court must examine each of the claims, which are directed to different statutory classes of subject matter, and determine whether or not each claim is patentable.

And I'm just addressing that briefly because it is important in some contexts; for example, in the double patenting issue, which I will address later. Claim 23 is directed specifically to a method of treating schizophrenia. And in a double patenting analysis, we look at the claims in the prior patent and see if there's a claim that would have rendered that claim obvious. So it makes a distinction in the double patenting analysis.

I would now like to discuss briefly the unique properties of aripiprazole. As discussed, Claim 12 recites the chemical formula for aripiprazole. And the defendants

concede that the prior art does not specifically disclose the chemical structure of aripiprazole.

They further concede that there was no antipsychotic in 1988, nor is there 22 years later, having the various structural attributes found in aripiprazole.

If we could turn to the next slide.

For example, the defendants do not dispute that aripiprazole is the only carbostyril derivative to be FDA approved. It is the only FDA-approved antipsychotic having a butoxy linker. And it's the only FDA-approved antipsychotic with a 2,3-dichloro substituted phenyl ring.

The defendants also concede that aripiprazole possesses a combination of pharmacological properties which make an exceptional compound for treating patients with schizophrenia and other mental disorders.

If we can go to the next slide.

The defendants do not dispute that aripiprazole is the only partial dopamine agonist to receive FDA approval as an antipsychotic. It's the only FDA-approved antipsychotic --

THE COURT: Does partial dopamine agonist -- it doesn't show it in the spec for the '528 patent; does it?

MR. MONROE: The specification does not address that particular property, though it is an inherent property of that compound, which was unexpected, and distinguishes it

from the prior art.

THE COURT: But that only shows up in the pharmacology and not in the patent material?

MR. MONROE: That is correct, Your Honor.

THE COURT: Okay.

MR. MONROE: It's also the only FDA-approved antipsychotic that exhibits functional selectivity, and it's the only --

THE COURT: By which you mean you can agonize the autoreceptor and antagonize the postsynaptic D2? Is that what you mean, or something else?

MR. MONROE: In part. You can actually -- it is receptor-specific and can go to specific receptors in combination, and not just to a single receptor.

THE COURT: So that refers to the heat map and all the different places that it goes?

MR. MONROE: That's correct, Your Honor.

I'd like to show that. The next slide is the heat map.

THE COURT: I didn't mean to interrupt you.

MR. MONROE: That flows right into the point that it's the only FDA-approved product which has that unique combination of properties that was shown in the heat map to which Dr. Roth testified.

As this slide demonstrates, which is PD-907 and was

PTX-406 at trial, aripiprazole exerts an amazingly complex action on receptors in the brain. These properties render it distinct from any other antipsychotic drug. And these complex properties make aripiprazole such an effective drug in a way that could not possibly have been predicted in advance.

The defendants have no real response to that unique aspect of aripiprazole. The defendants also do not --

THE COURT: Is this directly related to evaluating obviousness?

MR. MONROE: Yes, Your Honor. It comes in the context of unexpected results in the sense of secondary indicia of nonobviousness.

And it also identifies that this compound is something that didn't come before, and that no one would have expected this sort of product to have the properties which it has, looking at the prior art.

They also don't dispute that it represents a major medical advance due to its ability to treat schizophrenia and other mental disorders while maintaining a favorable side effect for the file.

If we could show slide PD-908.

This identifies some of the clinical advantages of aripiprazole, where you find -- and this was all addressed at trial and is on our posttrial findings, Your Honor. You find

clinical advantages like less sedation, reduced propensity to cause EPS or tardive dyskinesia, which was an extremely severe issue for schizophrenia patients. Also, lower risk of orthostatic hypotension and additional items mentioned in the slide.

Nor did they dispute that as a result of its unique properties, it has helped millions of patients around the world and has been approved for numerous indications beyond the treatment of schizophrenia.

If we could show the next slide, please.

This slide, as noted at trial -- this is PD-909 -- identifies all the various indications for which aripiprazole has been approved as additional research has been conducted on the compound to identify why it is so unique.

The defendants also do not dispute --

THE COURT: But you can't argue any of this material when you either apply for your patent or apply for your reexamination, per se; can you? Or you didn't?

MR. MONROE: That's correct, Your Honor. We didn't.

THE COURT: I get it.

MR. MONROE: But now it has come to have these unexpected properties and these uses.

And under the case law, that is something that a Court can look to to evaluate the uniqueness of a compound in an obviousness analysis from a secondary consideration

standpoint.

The defendants also do not dispute that as a result of its uniqueness, aripiprazole has won many prestigious awards, including the Prix Galien Award, which is the most prestigious in the pharmaceutical industry.

Nor do they dispute that it has met with tremendous commercial success. Indeed, it is that commercial success which drives their interest in copying aripiprazole in the first place.

Having made these concessions, the defendants attempt to ignore them, simplistically arguing that aripiprazole's unique chemical structure and accompanying unique pharmacological properties would have been obvious in view of Otsuka's prior own work with carbostyril compounds.

The defendants' efforts to establish such obviousness, however, are unsupported by credible evidence.

Now, to evaluate the obviousness of the claim, one must examine how a person of skill in the art, to which the patent is directed, would have viewed the state of the art at the time of the claimed invention, which in this case the parties have agreed is October of 1988.

As for the state of the art, Otsuka established at trial, and the defendants do not dispute, that the cause of schizophrenia was unknown at the critical date and, in fact, remains unknown today.

Nor do the defendants dispute that schizophrenia is a debilitating illness that severely impairs a person's ability to function.

Nor do they dispute, because of the seriousness of this illness, the entire industry was actively seeking at the critical date for new ways to treat this illness and, moreover, that such research continues today.

Again, this focuses on the long-felt and unmet need that the industry faced in trying to overcome the debilitating illness.

We established at trial, and the defendants do not dispute, several historical aspects of schizophrenia, which I won't go into detail today about.

For example, there's no real dispute that there was a first generation or typical antipsychotics, as we discussed at trial, but those have serious side effects; in particular, EPS.

The defendants also agree that the discovery of clozapine in the mid-1960s provided a ray of hope that caught the attention of the scientific community. But that excitement was short-lived when it was discovered that it had an extremely serious side effect.

It was such an exciting discovery because it would treat both the positive and negative symptoms of schizophrenia without the same -- with the lower propensity

to treat EPS, is probably the more fair way to say it.

THE COURT: With a lower propensity to cause EPS?

MR. MONROE: Cause EPS, that side effect. But that's probably a fair way to address it, since there was no EPS. It was just a lower propensity to cause that, and that was such a significant issue.

Clozapine took the scientific community by storm, so to speak, and that became the focus of everyone's research to try to figure out a way to develop another clozapine-like compound without those serious side effects, which was the -- agranulocytosis was the particularly bad side effect that clozapine had.

The safety issue, as I said, began or motivated researchers to try to find clozapine-like compounds, but nobody knew why it worked the way it did. And, therefore, the research continued throughout the 1980s, and it was the 1970s and 1980s, and it was a particularly dry period for end results.

And in fact, if we could show slide PD-190.

As we showed at trial, there was this period that was a dry period for new research, and no new FDA-approved antipsychotics came on the market during that period.

THE COURT: Including not even clozapine --

MR. MONROE: Correct, Your Honor.

THE COURT: -- because of its very bad side effects?

MR. MONROE: Correct, Your Honor.

And ultimately, the demand was so great to have something that would work, the FDA approved it to be used in those really extreme situations.

Shortly after clozapine was approved, a couple of years after that, another compound called risperidone was approved, which we discussed at trial. And that was chemically structurally different from clozapine, but it was designed to try to mimic the properties of clozapine.

Otsuka also established at trial that those skilled in the art, as I noted, were focusing on clozapine. And the defendants do not dispute that one skilled in the art would look to clozapine as a lead compound for antipsychotic research.

If we could turn to PD-911.

As Dr. Press testified at trial, clozapine is a truly remarkable lead compound. And in fact, Dr. Press also testified that it was the subject of everybody's research at that time. And in fact, he himself did research with respect to clozapine derivatives, and that was his background in this area.

As I noted, there was also the discovery around this time of risperidone.

And if we could turn to the next slide.

We showed this slide at trial to show some of the

abstracts that were published reporting on the discovery of risperidone, and noting that risperidone treated both the negative and positive symptoms of schizophrenia without the negative side effect of EPS.

And just as a coincidence, this report for risperidone can be contrasted with the report on OPC-4392 in which that abstract only reported that 4392 could treat negative symptoms and not the positive symptoms. And Dr. Press also admitted that these discoveries with risperidone were very promising in the scientific literature.

If we could go to the next slide, please.

THE COURT: Why did you put up 4392?

MR. MONROE: That was part of the slide that we used at trial, Your Honor, which contrasted what was being reported about 4392, which focused solely on the negative symptoms. Whereas what was being reported at that same time for risperidone was the fact that risperidone would treat both positive and negative symptoms.

THE COURT: Okay.

MR. MONROE: Contrasting how one skilled in the art would view those compounds when trying to decide what to pursue in an antipsychotic drug development program.

And as far as what Dr. Press had to say about risperidone, this is one excerpt, which is PD-913, in which the question was whether or not Dr. Press, by October of

1988, agreed that risperidone appeared to have the desired activity and safety profile of an atypical antipsychotic in preclinical and clinical reports. He said:

"I believe that risperidone was at a stage of development where it was in the clinic and was showing good effect."

Thus noting, again, that this was something in the art that people were aware of as of the critical date.

As noted, the defendants don't really dispute Otsuka's evidence at trial that the most likely lead compounds one of skill in the art would have chosen would have been either a clozapine-like compound or a risperidone-like compound. Instead, they argue you would also look at these other lead compounds.

But again, the test is, why would you choose one compound over what was also in the art, and how would the skilled artisan look at those various compounds and make a decision as to what to pursue in a drug development program? That's the real Daiichi test that controls this case.

And as a subset of that, which I noted previously, even if you assumed one skilled in the art would look to carbostyril compounds, the defendants haven't shown why you would choose their particular carbostyril compounds over the other carbostyril compounds that were in the prior art which showed better properties than their lead compounds.

Now, the hindsight analysis the defendants have engaged in is -- as we noted in the opening statement at this trial and also throughout trial, is the defendants start with aripiprazole, work backwards, and try to find something that looks like it, as close as they can, and then try to develop a theory as to why one would go from that structurally similar compound to aripiprazole. And that's not an appropriate analysis for obviousness.

THE COURT: That may be how they work up a case as lawyers. That's not how they presented it at trial. They put it in the frame of the invented process.

MR. MONROE: That's correct, Your Honor. I think that highlights the problem. For example, on the issue of whether or not one --

THE COURT: And incidentally, if pressed, they might say that. But they never have to say that, and I would never ask them that, and that will never be in evidence, and it may not even be true.

MR. MONROE: I understand completely, Your Honor. I understand completely.

But I think it's a good point to note, when we were questioning their experts about their analysis, this theory that they supposedly had developed which relied so heavily on Nakagawa, they wanted to argue it would have been negligent not to use Nakagawa as, you know, a teaching.

They actually didn't even know how to find that declaration. None of their experts has ever seen a prosecution history, knew how to get one, knew how you would find the materials in there, especially in 1988, before the Internet age. None of them had any knowledge of the entire prosecution history. Rather, they were handed this declaration from the prosecution history.

So I think it is relevant in assessing the credibility -- I think it's appropriate to focus on that for purposes of analyzing the credibility of the theory that's been presented.

THE COURT: Okay. Let's stick to the issues. The point is that under the law, this person of hypothetical ordinary skill in the art hypothetically does have everything on his desk.

MR. MONROE: That's correct. And then you go to how they would interpret that.

THE COURT: Right.

MR. MONROE: That issue comes up in the context of the publication issue, but we'll leave that with our posttrial findings.

THE COURT: Okay. Go to your next slide.

MR. MONROE: I'm going back to PD-903, which we showed earlier, which is the Daiichi slide. And this shows that it is contrary to do this sort of reverse analysis,

which is what we believe they are doing. They're focusing on the structural similarity to overcome the failure to show any evidence of why one skilled would be led to aripiprazole.

Again, the proper analysis is to evaluate what the skilled artisan would have viewed as a lead compound over other compounds, and then show that the skilled artisan would have chosen that compound to move forward.

I'd like to go back to one thing I mentioned at the beginning about the experts and qualifications. And I don't want to delve into this too much. I just want to note the different qualifications of the experts that were presented.

And if I could show slide PD-915.

This is sort of a summary of the experts that were presented on certain issues.

We believe it is important, Your Honor, that Otsuka was the only party to present an expert with clinical experience, and that was Dr. Roth. That sort of experience, again, is important for interpreting these reports about clinical studies, the sorts of things that I mentioned at the beginning and we'll speak about later, like the Murasaki 1987 article, for example.

One of the reasons their experts didn't understand what was the activating agent and know what certain terms mean was because they didn't have that level of experience that Dr. Roth had to interpret that term of art.

Otsuka also presented two antipsychotic drug discovery experienced experts. And the defendants did present Dr. Press, who had 25 years ago some limited experience, again, focusing on deriving something from clozapine, which is our simple position of the case.

If we could go to PD-916.

Just in brief, the Court did qualify Dr. Roth as an expert in schizophrenia, antipsychotic drug discovery and psychopharmacology with its medicinal chemistry component because his qualifications bridge all of these technologies and science and put him in a position to have a better understanding of what one skilled in the art would do.

He has an M.D., a Ph.D. in biochemistry. He practiced medicine as a psychiatrist for more than 10 years. He has treated thousands of schizophrenia patients and has extensive antipsychotic drug discovery. There are lots of awards, but I will skip those.

If we can go to the next slide, PD-917.

Dr. Nichols similarly was qualified in medicinal chemistry and pharmacology, thus bridging the two sciences and having a better understanding of how one skilled in the art would interpret the prior art. And I won't go into all of his awards, either.

But I would like to simply note that he's actually done research with aripiprazole and antipsychotic drug

discovery and actually discovered drugs in treating schizophrenia which are now in clinical trials.

We request that the Court look at the qualifications of the experts in analyzing their testimony.

As for the lead compound issue, to get to the merits, the defendants are asking the Court to discard what the entire industry was focusing on during the relevant period, which was clozapine and risperidone. The defendants argue that the Court should look to Otsuka's carbostyril compounds, as I noted.

They identified in the pretrial order two lead compounds, the unsubstituted butoxy compound and 4392. They only mention the 2,3-dichloropropoxy compound in the context of their bracketing theory, which was because the patent disclosed both a 2,3-dichloropropoxy compound and an unsubstituted butoxy compound, that would somehow teach one skilled in the art to get to aripiprazole.

And it's noted in our posttrial submissions there was no evidence presented that someone would review those two compounds as a pair or bracket or associate them together to come to aripiprazole.

THE COURT: The 2,3 --

MR. MONROE: Dichloropropoxy.

THE COURT: -- dichloropropoxy, is it listed in the '416? I thought it was listed in the Swedish patent and the

German application, but not in the '416. Same difference.

MR. MONROE: That's correct, Your Honor, but there is a reference that has both of the compounds in it. And I'll look that up to be more accurate for you.

THE COURT: That's all right. It's not necessary.

MR. MONROE: But the point was they were not focusing on the 2,3-dichloropropoxy compound, but rather pursuing this bracketing theory, which the Federal Circuit has rejected as an analysis for obviousness.

Again, focusing on the lead compound issue, the Teva/Barr defendants originally were the only ones arguing this issue and saying it was an unsubstituted butoxy compound that one would pick. They base their argument on structural similarity and said that you can modify that to get to aripiprazole.

Again, we contend, in their hindsight analysis they have not identified any reason why one skilled in the art would look for a lead compound, such as the unsubstituted butoxy compound, and then modify it to get to aripiprazole. As discussed at trial --

If we could put up the next slide, PD-919.

The '416 patent specifically refers to the unsubstituted butoxy compound as an antihistamine drug.

If you're going to review the prior art, you have to review the whole of the prior art and the whole of the

reference. You can't just pick and choose the teaching you want and then ignore the others.

The '416 patent specifically recites claims directed to the method of producing antihistamine effect, and then includes what's in the group of compounds that would produce that effect the unsubstituted butoxy compound. Therefore, specifically identifying that compound as an antihistamine.

There was a separate set of claims that addressed CNS controlling activity. And the unsubstituted butoxy was not included in that claim, even if you were to interpret that claim as implicitly including schizophrenia.

Now, the defendants had argued that there was a list at the beginning of the '416 patent which mentioned various potential uses for the class of compounds. And again, it was a huge class of compounds. Otsuka essentially discovered carbostyril compounds. For the idea that you can't --

THE COURT: So it's not billions. It's 9 trillion?

MR. MONROE: Trillion. I may be thinking of the defendant claim.

But to get a genus, you're entitled to get a genus to a large class of compounds if you have discovered a new class of compounds that's not yet in the prior art.

The whole point of the patent system is to have someone tell something to the public and add something to the scientific community.

Otsuka did that by discovering that large class of compounds. That doesn't detract from their ability to then get additional claims, subgenus claims in that same patent, species claims in that patent, or even get a separate patent in which they discover a species or subgenus of compounds which have unique properties that could not have been predicted from that large class, such as 9 trillion compounds.

THE COURT: Even if it's within the range of anticipated purposes for the genus?

MR. MONROE: Yes, Your Honor. The "anticipated" word bothers me a little.

THE COURT: I'm so sorry. Stated. Stated purposes.

MR. MONROE: Correct. Correct.

And again, they provided no reason why someone would go to the '416 patent and focus on the unsubstituted butoxy as a lead compound for any psychotic research, given how it's specifically characterized in the patent.

THE COURT: No. They go straight to the Nakagawa declaration.

MR. MONROE: And that's where I would like to go next, Your Honor. The Nakagawa declaration also doesn't direct one to the unsubstituted butoxy compound.

Go to the next slide.

First, it's not prior art, but I'm leaving that for

our posttrial submissions. I'd like to focus on the science and then the technical issues.

As established at trial, the purpose of the declaration was to compare compounds of the invention of the prior art, not to provide structure activity relationship information.

And, therefore, this suggestion that one would find the Nakagawa declaration, then look at this declaration which had Mouse Jumping data, and immediately say antipsychotic test, and I'm going to then go to the unsubstituted butoxy compound, is unfounded because if you were looking at that declaration, and even if -- which we disagree -- would immediately think antipsychotic, even if you did, and you looked at that declaration, you would go to the most potent compound. That's the concept of looking for your best drugs, and it was not the unsubstituted butoxy compound.

And, therefore, the defendants kind of want to ignore that because they need the compound that looks just like aripiprazole, but for a couple of modifications, which turn out to be extremely important modifications and actually result in unexpected properties.

Again, the declaration on its face does not say what the purpose of that pharmacological test was for. You often conduct tests to compare compounds by using a test that is a conventional one to look at pharmacological properties. It

doesn't mean you're trying to establish that that compound had a particular property.

And in this case the declaration doesn't say what it's trying to prove, other than comparing a group of compounds to another group of compounds.

Again, looking at the declaration --

THE COURT: In that declaration, correct me if I'm wrong, the group that we're talking about, which included No. 44 and the unsubstituted butoxy, was being compared to noncarbostyrils in the prior art, I think. Is that right?

You know, Examples A, B, C, D, are those carbostyrils or not? I don't think so.

MR. MONROE: They were not carbostyrils, Your Honor. I wanted to confirm that before saying that. And they come from -- the prior art was U.S. Patent No. 4,210,753, for purposes of the record. That was the patent they were comparing it to.

THE COURT: Fine.

MR. MONROE: In addition, if you're looking at carbostyril prior art, one of the pieces of the prior art was the '932 patent, which was discussed at trial. And that discloses similar Mouse Jumping data to that found in the Nakagawa declaration.

And if you look at that patent, you would be directed to 6-position isomers with all carbon linkers, which were

significantly more potent than the unsubstituted butoxy compound of the Nakagawa declaration, again, leading away from the compound they identified as a lead compound.

So sticking with the lead compound issue, you then get to 4392. And Apotex was the one who originally contended that 4392 was a lead compound.

THE COURT: You get 4392 because that was in the literature at the critical data?

MR. MONROE: That is correct. And there is a dispute regarding what the literature taught one skilled in the art at that time. The defendants focus on some preclinical literature.

And Otsuka has pointed out that if you look at some of the clinical literature which was also in the prior art as of October 1988, it shows the 4392 actually was not achieving antipsychotic activity. It was not having that effect that was needed for treating schizophrenia. That's why ultimately, the compound was dropped and not pursued further.

THE COURT: Well, they say the phrase is "not strong." So at least it's something to like refer to --

MR. MONROE: That's their position, Your Honor.

And I think it's important to look to how Dr. Roth and Dr. Nichols, who have the expertise, and especially Dr. Roth, in looking at clinical reports, to know what that means -- what that language means when you're publishing it.

The concept of "not strong" means it didn't perform the goal that was intended.

For example, if we could go to slide PD-922.

With respect to the Gerbaldo paper from March of 1988, that abstract noted that 4392 affected the negative symptoms in clinical studies and did not indicate that it treated positive symptoms.

Dr. Roth interpreted the silence on positive symptoms as indicating that there was no effect because that's how these sorts of reports get published. You identify the positive effect that you obtain, and they did not identify one in this report.

Similarly, Dr. Roth interpreted the 1987 Murasaki paper as indicating that there was no activity given that nonstrong language that you just noted, Your Honor.

And Dr. Press even admitted at trial that when he said in his expert reports that 4392 had strong antischizophrenic activity, he had not even considered the 1987 Murasaki paper. So he had formed his opinion about the strength of 4392 without having looked at all of the art until closer to trial.

Dr. Roth also noted that the reference to "strong activating action" would have been a red flag for people who treat schizophrenia and would have directed one away from 4392.

And as I noted earlier, Dr. Press did not know what that term meant, did not know whether it was a good thing or a bad thing.

Further confirming the failure of 4392 in the public eye, the 1988 Murasaki indicated that 4392 would not be safe in therapeutic doses. Dr. Roth explained that that paper noted that in clinical trials 4392 caused numerous serious side effects and, therefore, the skilled artisan would not have been encouraged to pursue 4392 or any carbostyril derivative as a potential antipsychotic.

Again, all of this information was public knowledge as of the critical date. And to suggest that one would have chosen 4392 as a lead compound in the context of this public information is really contrary to what one skilled in the art would do.

In fact, that's not what Otsuka did, as shown through the testimony at trial, where Dr. Oshiro went back to earlier compounds and did not start the 4392, as defendants keep alleging.

The last lead compound is, again, the 2,3-dichloropropoxy. And I've addressed the bracketing issue already, Your Honor. And if you look at it as a lead compound, that theory also is baseless, based on nothing but pure hindsight.

The defendants point to the Swedish '945 publication

and the German '105 publication, which disclosed this compound amongst several hundred compounds.

If we can go to PD-923.

The Swedish '945 application is largely the same as the related '416 patent. It fails to describe the 2,3-dichloropropoxy compound as an antipsychotic. It provides no test data relating to antipsychotic activity. And like the '416 patent, antischizophrenic activity is one of ten possible therapeutic uses that are described. It doesn't identify which compounds, if any, are antipsychotics.

And the 2,3-dichloropropoxy compound is the 22nd of 86 different compounds listed in Example 134. In other words, it's one of many compounds, and the defendants have not shown why one would have focused in or zeroed in on that compound for purposes of a lead compound.

And similarly, the German '105 patent, which is a counterpart to the '416 patent, doesn't even include the passing reference to schizophrenia found in the Swedish '945 patent.

In summary, with respect to the lead compound issue, one skilled in the art would not have picked as a lead compound for antipsychotic research any of the three compounds cited by the defendants. Instead, the skilled artisan would have pointed his research in a different direction. And we presented a lot of evidence at trial to

that effect.

And again, that is the issue that is before the Court as a threshold matter under the Daiichi case from the Federal Circuit.

And then I think it's important to note that except for Otsuka's structurally unique aripiprazole, all new antipsychotics to gain FDA approval since 1975 have been similar in structure to either clozapine or risperidone.

Go to slide PD-924, please.

And this was a slide we showed at trial to again highlight that you had clozapine, which was a breakthrough pioneer compound, and then color-coded you see the progeny, what people were doing.

You had risperidone, which was the breakthrough pioneer compound, and its progeny in blue, and then you have aripiprazole, which stands alone. And even after all these years and after a lot of research, there is not yet a derivative of aripiprazole. Again, identifying how unique it is and how hard it is to find a particular compound having the same sort of properties.

As for the modifications --

THE COURT: If you were to take -- and I'm not going to burden this record much -- but if you were to take aripiprazole and take off the two chlorines and put two CHs on there --

MR. MONROE: Methyls?

THE COURT: -- methyls -- could you get a patent on that today, even if it would be a good antipsychotic drug?

MR. MONROE: Well, like any patent lawyer, I will say I would have to look at the prior art and see if the prior art actually specifically discloses that compound. I would have to assess whether that compound, if it was not disclosed, actually showed some unexpected properties or something that would not have been expected.

And you would have to analyze whether or not those structural changes would have expected whatever the properties you ultimately ended up with were because those small changes -- we showed at trial small changes, one chlorine, can completely eradicate all activity. It just depends on where you put it.

So I can't really answer that question without all of those facts.

As for the modifications, I'll try to address those as succinctly as I can, Your Honor.

THE COURT: Where are we now?

MR. MONROE: We are now --

THE COURT: What's the topic?

MR. MONROE: -- moving on to modifications of the lead compounds.

THE COURT: Oh, okay.

MR. MONROE: Even assuming their lead compounds were appropriate, what would have led one to get from those lead compounds to aripiprazole other than hindsight or structural similarity arguments?

As for the unsubstituted butoxy compound, there is no suggestion in the '416 patent to add a chlorine atom at the 2- and 3-position of the phenyl ring to convert it from an antihistamine to an antipsychotic. To the contrary, the '416 patent discloses numerous compounds, and none of those compounds have such a structure.

And as Dr. Nichols established at trial, those compounds -- sorry -- chlorination is not required for antipsychotic activity. And there was no known antipsychotic as of October of 1988 with a 2,3-dichloro substituted phenyl ring, and there is none today.

Dr. Press even admitted that he has authored papers in which chlorination reduced or completely eliminated a compound's potential antipsychotic activity. Therefore, one can't simply assume that you would add a chlorine and get a particular result.

The defendants point to the Nakagawa declaration as their primary teaching for modifying the unsubstituted butoxy compound.

And if we go to PE-920, which we looked at earlier.

The defendants argue that the declaration includes a

propoxy linked compound with a 2-chloro substituent on the phenyl ring and another compound with a 3-chloro substituent, and both of these were more potent than any unsubstituted propoxy compound.

The defendants have provided no evidence, however, that a propoxy compound with both substituents would be equally or even more potent than the monosubstituted compounds or that such potency translates from propoxy compounds to butoxy compounds.

Again, as a reminder, the Nakagawa declaration only evaluated unsubstituted or monosubstituted compounds, as shown in the slide. It did not analyze disubstituted compounds or disclose them, even.

And eight of the nine compounds tested in the Nakagawa declaration had a propoxy linker, not a butoxy linker; thus, again, teaching towards propoxy linkers if one were to engage in the sort of SAR analysis the defendants contend one would do.

Our testimony at trial established that's not what you would do. But assuming their hypothetical, you would get to a different result than they have proposed, and you would not be led to modify the unsubstituted butoxy compound to have a 2,3-dichlorophenyl ring. In fact, compound 44 of the Nakagawa declaration was ten times more potent than the unsubstituted butoxy compound.

An issue that was raised at trial and in the opening is that the defendants make a lot of arguments about what would happen if you did X, Y and Z, but did not present any evidence through testing to establish their position, which they could easily have done given their burden of proof.

And again, as I noted, Dr. Press admitted that chlorination can have different effects and, therefore, you wouldn't assume that having two of them would give you an additive effect. There's no basis for that in the literature in support of that, and his testimony is contrary to that conclusion.

Moreover, the Banno article which was discussed at trial specifically reports that:

"The introduction of dichloro substitution at the 2- and 3-positions on the phenyl ring of the 2,3-dichloropropoxy compound significantly reduced activity in the Mouse Jumping Test."

And that highlights Dr. Press' additive theory is entirely unfounded.

The defendants also rely on the Swedish '945 application, but that also doesn't support their modification issue for the unsubstituted butoxy. It does disclose a 2,3-dichloropropoxy compound, but that's all it discloses. It doesn't compare it to an unsubstituted version or provide any guidance on the impact of that chlorination. Nor is

there any data suggesting that the compound is an antipsychotic.

The skilled artisan, therefore, wouldn't look to the Swedish '945 disclosure as a way to modify the unsubstituted butoxy compound.

And finally, with respect to the unsubstituted butoxy compound, the Hiyama abstract similarly fails to support the defendant's position.

If we could go to PD-925.

The Hiyama reference mentions another Otsuka compound, which is OPC-4139. It had a propoxy linker, not a butoxy linker, and it was monosubstituted on the phenyl ring with a single chlorine at the 3-position. It was not disubstituted. And there was no suggestion to modify that compound in any way or that you should modify any other compound through the teachings of 4319 [sic].

Moreover, it's important to note that 4139 was shown to be inactive in the Apomorphine-Induced Stereotypy Test. And as Dr. Roth explained, it's devoid of any postsynaptic D2 antagonist activity. And, therefore, there is no reason one skilled in the art would look to that compound, which was inactive in the appropriate test, as a way to modify the unsubstituted butoxy compound.

With respect to 4392 and its status as a lead compound, a lot of the same arguments apply. But I would

like to point out a few particular points on 4392 and why one skilled in the art would not be led to modify it in the way suggested by the defendants.

THE COURT: Are we on 4392 again?

MR. MONROE: We're back to 4392 as a lead compound and its modification.

THE COURT: Okay. Have you returned to a different slide or --

MR. MONROE: Not yet, Your Honor. In just a moment.

The defendants conceded that there are multiple modifications you have to make to 4392 to get to aripiprazole, and those multiple modifications are simply a few among thousands one could do with attempting to modify 4392.

And Dr. Castagnoli admitted at trial that all of the structural features of 4392 are associated with its clinical profile and side effect profile, and that the prior art did not describe which changes to its structure could be made without negatively impacting its side effect profile. You just don't know until you try to make modifications.

Dr. Castagnoli spoke in vague terms about how he thought a skilled artisan would try to "tune down" the autoreceptor agonist activity of 4392 or "pump up" the antagonistic activity. And today we've heard the term "boost" activity. But he could not explain how the skilled

artisan would actually go about doing such tuning and pumping.

The defendants, therefore, point to the Wise poster, which was discussed at length at trial.

And if we'd go to PD-926.

Again, that's not prior art, but we will leave that with our posttrial submissions, Your Honor. Assuming it were, it would not have led one skilled in the art to modify 4392 in the manner that the defendants contend.

It concerns a class of compounds known as coumarins. And one of ordinary skill in the art, as Dr. Nichols testified, would not have assumed that the biological properties of coumarins would translate to carbostyril derivatives as an overriding general proposition.

Moreover, the Wise poster specifically teaches away from aripiprazole. Wise identifies its new class of coumarins as dopamine autoreceptor agonists. By October of 1988, however, the autoreceptor agonist theory had been tested with numerous compounds, and all failed in treating schizophrenia.

Accordingly, one looking to develop an antipsychotic with D2 receptor antagonistic activity would have had no reason to look for assistance from the Wise poster directed to autoreceptor agonists.

Indeed, Dr. Castagnoli never explained why one

looking to tune down the autoreceptor activity of 4392 would look to a paper whose main theme was to improve autoreceptor activity. The Wise poster does not even mention D2 antagonistic activity or any test used to evaluate that activity. Indeed, Dr. Roth pointed out that Dr. Castagnoli's testimony that the LMA Test measures postsynaptic D2 antagonism was incorrect.

In that regard, Otsuka's posttrial submission lists several other instances in which Dr. Castagnoli's testimony regarding the Wise poster was in error, as shown by the testimony of the defendants' other expert, Dr. Marshall.

In addition, the Wise poster focuses in and spotlights compound 116,795, which has no substituents on its phenyl ring, and specifically states in the abstract that addition of chloro or methyl substituents to the phenyl portion of the phenylpiperazine resulted in complete loss of DA, which is dopamine, agonist activity.

Similarly, the heading in Table 2 of the Wise poster stated that incorporation of substituents on the phenyl ring resulted in loss of DA and agonist activity.

Finally, the summary at the end of the poster stated that no substituents on the terminal phenyl ring are required for DA agonist activity, which is sensitive to structural modifications.

The defendants improperly disregard these three

explicit statements which note that substituents on the phenyl ring result in a loss of DA agonist activity, which was the focus of this paper, and contend contrary to these statements that the skilled artisan would have interpreted the 3-chloro substituted phenyl compound in that paper as teaching the chlorination of the phenyl ring, which was completely contrary to the whole teaching of that paper. It simply makes no sense.

It's further noted that the key compound which Wise focused on was a propoxy linked compound, and it is identified as the key and most promising compound.

Thus, Wise would actually have led one skilled in the art to modify 4392 -- would not have led one of ordinary skill in the art to modify 4392 to have a butoxy linker. Rather, it confirms that one would look at a propoxy linker. But again, that's assuming one would even look at coumarins, which we dispute.

And then moving on to the '456 patent, that was also discussed at trial briefly. It discloses coumarins and describes a compound with a 2,3-dichloro substituted phenyl group. No test data are provided for this compound, and there's nothing in that patent which would have led anyone to focus on that particular coumarin compound.

Moreover, the only compounds tested for potential antipsychotic activity in the '456 patent were propoxy linked

compounds with no substituents on the phenyl ring. And the only compound claimed in the '456 patent for treating psychosis was a coumarin with a propoxy linker with no substituents on the phenyl ring.

Again, like the Wise poster, the '456 patent, even if relevant for its coumarin teachings, would teach away from modifying 4392 to arrive at aripiprazole.

As for the Nakagawa declaration and its role with respect to 4392, Dr. Nichols testified that there is no teaching therein that would suggest that you modify 4392 in any way.

Indeed, there's nothing in the Nakagawa declaration which would have led the skilled artisan to convert the propoxy linker of 4392 to a butoxy linker and then change the 2,3-dimethyl substituents to 2,3-dichloro substituents.

First, one would not have attempted to draw any SAR conclusions. We dispute, as presented by our experts, that position of the defendants.

Moreover, the defendants did not present any evidence that the ED50 values for the butoxy linked compound and the propoxy linked compounds were significant --

THE COURT: Would you back up, please.

MR. MONROE: Yes.

THE COURT: Start that sentence over.

MR. MONROE: Okay. The defendants did not present

any evidence that the ED50 values for the butoxy linked compounds which had a 5.5 number, and the propoxy linked compound which had a 9.5 number -- 9.3 number, were significantly different. There was no evidence that those two compounds were actually significantly different and, therefore, wouldn't have taught anybody to choose one over the other.

Nor was there any Mouse Jumping data in the prior art with respect to 4392. And thus, one could not compare what 4392 would have been in that sort of test compared to the compounds in the Nakagawa declaration.

Therefore, one skilled in the art would not have reached any particular conclusion by looking at the Nakagawa declaration which would relate to modifying 4392.

Just as an example, Dr. Castagnoli admitted that one skilled in the art would not have any reasonable expectation as to what might happen if test compound 39 of Nakagawa, which had the single chlorine at the 3-position, what would happen if it were modified to have a second chlorine at the 2-position. There's no evidence to establish how one would actually combine those two aspects of the structure in importing it over into 4392.

Finally, with the 4392 and modifications of that compound, the defendants also contend that the '416 patent would have suggested to the skilled artisan to make both

carbostyril and dihydrocarbostyril versions of 4392.

The '416 patent doesn't refer to 4392, and the defendants have failed to explain why one skilled in the art would pick this particular teaching out of the '416 patent for purposes of modifying 4392 while ignoring all of the other teachings.

Again, you have to look at all the teachings of a piece of prior art in assessing how you would modify the other pieces of the prior art.

The only additional comment I'll make from a modification standpoint is with respect to the 2,3-dichloropropoxy compound.

And just briefly, again, there has been no teaching as to why one would be led to modify the 2,3-dichloropropoxy compound to get aripiprazole other than defendants' arguments regarding structural similarity, which is improper.

In sum, the defendants resort to a routine optimization argument --

THE COURT: Well, they say it's a homolog. It's just the next -- you know, it's just the next -- add one -- add a link. There you are.

MR. MONROE: And that is an inappropriate analysis, Your Honor, under Federal Circuit case law. Homology does not result in a prima facie case of obviousness and contrary to defendants' position. And I'll address a couple of cases

on that point a little bit further.

The defendants point at this routine optimization as a way to get around the no teaching in the actual literature as to what to do.

THE COURT: Okay. They say the routine lab work to, you know, move a set of experimental compounds down the line isn't patentable. So --

MR. MONROE: That's their position, Your Honor.

THE COURT: So they say that that's what this was.

MR. MONROE: We disagree that that's what happened here. We think the evidence established that's not what happened.

And you have to look at what one would expect to do in modifying a compound and why one would be led to modify that compound in a particular way because you don't know what the result will be.

Basically, nothing would be patentable in the chemical arts if you could simply argue, hook something up to a computer, and get every compound you possibly can and test every compound you possibly can. That's not the standard.

THE COURT: I know. I'm still back at the 9 trillion compounds.

MR. MONROE: 9 trillion compounds.

And again, if it was -- I would like to know, if it was as simple as the defendants said, then Otsuka would

simply have immediately designed aripiprazole. Otsuka had the most experience with carbostyril compounds.

That's not what they did. They had to actually go through a process and try to discover something that would have the properties they wanted. And I won't go through all those details again, but those details highlight that it's not as simple as they want to suggest it is.

And in fact, if it were that simple, others would have come up with derivatives of aripiprazole that are very effective and promising as antipsychotics, and that hasn't happened.

THE COURT: I don't quite understand the little argument that you make, which is, "Oh, yes, our patent '416 really did not block innovation by others." But you'll get there, so I'll wait.

MR. MONROE: I will. Yes, Your Honor, I'll address that for you. That comes up in the secondary considerations, which I was just moving to. We provided a lot of extensive evidence about secondary considerations. I won't go into all of that.

THE COURT: That's all documented.

MR. MONROE: Right. That's in the posttrial submission.

We did show unexpected results, which is an important issue in this case, and I would direct the Court to those

proposed findings. And we showed that small changes make big differences, and that structurally similar compounds can be very different in their properties. And that's the hallmark of nonobviousness. We also showed the widespread adoption of the compound and its commercial success.

They have attempted to rebut some of the secondary consideration arguments on the basis of the blocking patent issue.

I'd like to first note that the '416 patent issued in March of 1988. And so from the standpoint of long-felt need and unmet need, the blocking patent doesn't really affect that analysis because of all of that long-felt unmet need that occurred up until March of 1988.

So that evidence of long-felt unmet need, failure by others to what people would do, is still relevant even under their blocking patent argument, if you were to accept it. So that secondary consideration is still an important factor in the Court's analysis.

THE COURT: I hear the words, but I'm not sure whether you have now switched over to arguing double patenting or not.

MR. MONROE: Not yet. I'm still on secondary considerations and blocking and whether or not the Court can look to commercial success, for example, given their blocking patent theory.

The simple answer to the blocking patent theory is there's no evidence that anybody was stopped from getting in the sandbox, as it was referred to.

In fact, Teva got in the sandbox. Teva researched and filed its own patent applications directed to polymorphs of aripiprazole. That is striking evidence that no one was blocked from doing research in this area.

THE COURT: Well, I think what they're saying is, well, at some point the '416 patent went into the Orange Book for aripiprazole, but that was much later.

MR. MONROE: That is correct, Your Honor.

THE COURT: But they're saying that once the '416 patent comes out, there's not a commercial motivation to do research because you're going to get such a pushback from Otsuka. You'll be accused of trying to infringe the '416 patent, even if you can raise some credible arguments to have a species or subgenus patent approved for yourself in the wake of the '416. I think that's what they're saying.

MR. MONROE: I believe that's the theory that they presented without providing any support that that is actually what happened in this case.

And the facts of what actually happened in this case show that Teva wasn't blocked, and Teva did pursue research with respect to aripiprazole.

THE COURT: With respect to carbostyrils and

aripiprazole?

MR. MONROE: With respect to aripiprazole. They --

THE COURT: So aripiprazole, the '528 patent, isn't a blocking patent to more aripiprazole research efforts, is what they're saying.

MR. MONROE: That's exactly -- that's what the patent office has concluded.

THE COURT: But they're saying that the '416 really had a freezing -- not a chilling, but a freezing effect.

MR. MONROE: And the argument -- our argument, Your Honor, is if you look at what's really blocking, I mean, if you were willing to fight against a patent specifically directed to aripiprazole and do research directed to aripiprazole in the sake of a patent that specifically recited it, that undercuts an argument that some broad genus claim prevented you from pursuing carbostyril compounds. Then as a practical reality, nothing stopped you from pursuing something that was specifically patented.

But you're arguing, on the other hand, that there's this shadow of carbostyril patent. This carbostyril patent prevented you from pursuing any research.

THE COURT: I think I understand your point.

MR. MONROE: And as far as the double patenting --

THE COURT: Have we finished 103, obviously?

MR. MONROE: That's correct, Your Honor. And I'm

done with secondary considerations, and moving into double patenting --

THE COURT: Okay. Before you --

MR. MONROE: -- unless you have any questions.

THE COURT: No, I don't. But before you address double patenting, I really have a question for both sides. And I know Ms. Holland is going to have something to say when you're done.

But my sort of working understanding of the Federal Circuit doctrine of obviousness type double patenting is a judge-made doctrine. Right?

MR. MONROE: Correct.

THE COURT: My understanding of it is that it does not arise except where you have an original application before the patent office that becomes divided through the history of that application, such that all patents that eventually issue derive their direct ancestry and their specification from that original application.

That's the only context in which I have seen obviousness type double patenting arise in cases that I have read or decided.

So I need to be assured that we can really talk about the concept of obviousness type double patenting, whereas here, the '528 patent does not derive from the application for the '416 and, in fact, the '416 patent was already fully

issued and in the public domain before the application for the '528, with its own separate specification, was filed at the patent office.

Have I made my question clear?

MR. MONROE: I think your question is clear, Your Honor.

And I believe you are correct that the cases have addressed -- the case law has addressed double patenting in a context of continuing applications that one can file in terms of disclaimers to overcome that rejection.

It may be against my interests on this issue, but I will note that conceptually I could see a scenario in which, if one filed applications on the same day, for example, and didn't say they were related to one another, but filed the exact same claims, that would be a statutory double patenting situation.

And in fact, if you filed two applications on the same day with slightly different claims, then there could be the potential for an obviousness type double patenting rejection.

I am not aware of a case dealing with that. But that would be my frank answer to your question.

THE COURT: Okay. So, then, what is your answer to the question that I pose, which is: Is this a case where obviousness type double patenting analysis enters in, based

upon what we know as the application history of the '416 in comparison to the '528?

And Ms. Holland, you'll get your chance. I'm asking Mr. Monroe.

MS. HOLLAND: I'm ready for it.

THE COURT: I know you are.

MR. MONROE: Our response, Your Honor, has been that you don't even get to double patenting because the '416 patent is prior art because, as you noted, it was filed earlier. It became prior art. It was in the public domain. And the double patenting is just subsumed by the obviousness analysis under Section 103.

THE COURT: And you're not aware of any case law that would sweep this kind of situation into the double patenting theory?

MR. MONROE: I am not personally aware of that, but I can look into that. I'm not arguing it does not fall within that. I am just not aware of a case that would address that.

THE COURT: Okay. But still, you're going to address it for argument's sake here. Go ahead.

MR. MONROE: Correct. And for purposes of double patenting, I think we need to deal with a couple of issues.

First, if we could have slide PD-930.

Contrary to defendants' position, Otsuka did not patent aripiprazole twice. Their argument suggests that we

actually specifically claimed aripiprazole in the '416 patent. That did not happen. The '416 patent is directed to a genus and discloses a number of compounds, but doesn't disclose aripiprazole.

An Otsuka scientist discovered aripiprazole, a single compound, within that huge genus. That's allowed under the law when you find something special and new that wouldn't have been predicted from that big group of compounds that you had originally patented.

THE COURT: All right. But while the '416 patent existed, all 9 trillion compounds were covered by that patent?

MR. MONROE: That is correct, Your Honor.

THE COURT: Whether or not they were specifically listed in the disclosures of the patent?

MR. MONROE: Right. All 9 trillion compounds were species within that genus of 9 trillion compounds.

And the question is, how would one have -- under a double patent analysis, you look at the claims of the '416 patent and then evaluate how would one of ordinary skill in the art been modified to modify what's in that claim to come to the claim in the patent-at-issue.

And that's how you get to some of the same arguments that we've heard under the 103 obviousness case.

And just to give you some case support, Your Honor,

turn to the next slide, which is PD-931.

In re Baird is a Federal Circuit case which specifically notes that the fact that a claimed compound may be encompassed by a disclosed generic formula does not by itself render the compound obvious.

THE COURT: I'm sure that's true, or the patent office wouldn't be issuing species patents.

MR. MONROE: That's exactly right, Your Honor.

And it's also important to note with respect to, like, the structural similarity arguments that came up in the context of the Hirose declaration, Mr. Van Horn's submission to the patent office did not admit that there was a prima facie case of obviousness based on structural similarity.

Rather, he noted that it's possible that one may argue that, which he debated and throughout the prosecution contended against and said that was not fair. But for purposes of resolving that issue, Otsuka presented evidence of unexpected results.

So I just wanted to address the issue that defendants had made that he had somehow admitted that there was a prima facie case, which is not correct.

Then if I could have the next slide.

Again, courts have repeatedly found chemical compounds' nonobviousness over prior art genus. And I think the Eli Lilly case is particularly informative in this case

because it -- a couple of things happened.

First, in that case, a claim to the antipsychotic drug olanzapine was held nonobvious in light of Lilly's prior art, the '574 patent, that claimed a genus encompassing olanzapine. Olanzapine was also found to be not obvious in light of the next adjacent homolog specifically disclosed in the '574 patent. Again, this concept that homolog is not enough to render unpatentable a compound.

The Court also rejected the defendants' bracket theory as simply characterizing structural similarity, which is not what controls this sort of analysis.

And then finally, the Federal Circuit did not specifically address, but did affirm the case ultimately. And at the district court level, the district court had held that double patenting was subsumed by the obviousness.

If I could go to the next slide.

Similarly, I'd like to identify the Sanofi case against Apotex in which a claim to a pharmaceutical compound was held nonobvious in light of a generic disclosure in claims in Sanofi's prior '596 patent. And again, in that case the district court had held that the obviousness inquiry was subsumed by obviousness inquiry.

THE COURT: That the double patent was subsumed by the obviousness.

MR. MONROE: Yeah. Sorry. I misspoke.

And finally, with Takeda, in that case the Federal Circuit found that a claim to a diabetic drug was not obvious over Takeda's prior art patent that included generic claims the company had for this compound.

Again, I wanted to bring those to the Court's attention for purposes of addressing the defendants' contention that there's somehow something wrong with getting a species claim or a subgenus claim in the face of a prior genus claim.

I'd like to quickly address now the --

THE COURT: I don't think they really say that. I just think they say that this wasn't novel; that inventively, you could take what you had in the prior art and get to aripiprazole without a lot of effort. So it's not patentable. It's obvious.

MR. MONROE: Well, I think it's the --

THE COURT: I don't think they're saying you couldn't get a species patent after the '416. But thank you for the case.

MR. MONROE: I hope you're correct that they're not saying that, Your Honor.

With respect to enforceability, I'll just briefly touch upon the four issues that Ms. Holland identified.

As far as the allegedly inconsistent stereotypy data, this argument was not in the pretrial order and shouldn't be

addressed. But even so, the defendants have failed to establish the existence of any inconsistent data.

During cross-examination Dr. Oshiro was asked about some internal data regarding the testing of aripiprazole and the 2,3-dichloropropoxy compound in an Anti-Apomorphine Stereotypy Test back in 1987. This data indicated that aripiprazole was six times more potent than the 2,3-dichloropropoxy compound in that particular testing.

And the defendants contend that this is inconsistent with the data in the Hirose declaration showing a 23-fold difference.

There is no evidence, however, concerning the test conditions underlying the internal test data back in 1987 and whether the resulting data may be validly compared to the Hirose data.

Rather than them presenting any evidence on that issue, the defendants mischaracterized the testimony of Dr. Oshiro, as we explained in our posttrial submission.

We contend he did not make that sort of admission that as a general proposition, all six-fold increases are not surprising. Rather, he was in context talking about whether or not he found something that was as surprising as what he found when he found the 15-fold increase in his research which led to his lead compound, 14542.

And moreover, there is no evidence that any

individual knowingly withheld this information. Dr. Oshiro admitted that he likely saw something -- a version of something that was submitted to the patent office during the reexamination, but he didn't recall what it was.

And there's no evidence that he specifically edited the final declaration that was submitted.

THE COURT: Well, they couldn't get that anyway. Right? Wouldn't that be privileged?

They say the privilege log says he's sitting around and had 300 contacts with this process. That's about the limit of the discovery they can get.

But go ahead.

MR. MONROE: I agree. And they made no efforts to go further, Your Honor.

I mean, Dr. Oshiro admits he was at certain meeting. But also, as noted, he testified he doesn't know what's happening at most of those meetings because he can't hear what's being said.

So to conclude that because he was in the room, he was aware of something, in this particular case is not appropriate.

As far as being on the privilege log, Dr. Oshiro did test --

THE COURT: I guess he does say, though, that he had various drafts of the -- what do you call it -- the

successive submissions to the PTO during the reexamination, and he probably saw the test results that were submitted in the reexamination. I think he was asked that.

MR. MONROE: He wasn't asked the very specific question I think you're going to, Your Honor. He was asked about what he would have seen. He couldn't recall seeing that particular declaration. He did say he saw something and had provided comments.

As he testified, his role as an advisor was to look at scientific issues and answer scientific questions. There's no evidence that he was involved in the actual formulation of that declaration and its content, and so I don't think they've shown that he had that knowledge.

Moreover, the defendants didn't ask him at trial, "Were you aware of this data back in 1987?" They didn't delve into a lot of questions about that data and what that data meant and what he knew about it.

THE COURT: You mean, were you thinking of it in 2008 --

MR. MONROE: '5.

THE COURT: -- '5 when it sat in your binder since 1987?

It was his binder. Right?

MR. MONROE: It was produced from one of his lab notebooks, which are stored not with him.

But they could have asked him a lot of questions. They could have asked Dr. Hirose a lot of questions to try to dig into this issue rather than just asking for an inference.

They fault Otsuka for not asking the questions they didn't ask or -- and that they didn't even ask at his deposition. They could have gone into some of this at his deposition, and they didn't.

THE COURT: Did they bring up the six-time difference at Oshiro's deposition?

MR. MONROE: No, Your Honor.

THE COURT: Okay.

MR. MONROE: And so there's been no evidence that anybody acted with deceptive intent and specifically withheld that data and what that data actually meant.

As far as the second issue that Ms. Holland identified, she talked about allegedly false descriptions of testing procedures. The particular phrase they focus on in Dr. Hirose's declaration was "an observer blind to the treatment received by the mice." And there was a lot of discussion about that at trial.

And Otsuka's position is that it's clear that Dr. Hirose acted with good faith, that those are the sorts of tests he always conducted, and that that statement is accurate. And the defendants' experts a couple of times admitted that the protocol had a blinding with respect to the

dose.

So that sentence was not inaccurate. It said there was a blind to the treatment. And the dispute is, what does "treatment" mean? And defendants want to argue that term as meaning something different than what Dr. Hirose meant when he used that term.

In addition, they want to argue that there was only -- that the sentence suggests there was only one person, when there were actually two. If you look at the face of the protocol, there's two individuals involved.

And the testimony at trial from the experts established that one skilled in the art and someone at the patent office would assume by looking at the protocol that have the two individuals listed, that two people were involved.

And what they would interpret that sentence to mean is that one individual would analyze one particular mouse, which is exactly what happened. There were two individuals who looked at their individual mice.

So this is completely accurate. There's no evidence of any intent to mislead the patent office regarding how the test protocol was conducted.

Moreover, there's no evidence that that test protocol led to any errors in the data or any problems. Everything is this inference or suggestion that this data must somehow be

wrong. But again, the defense could have conducted their own tests and established that it was wrong if it truly was. They didn't. Rather, they just want to argue an inference.

And Dr. Thisted, our statistician, looked at the data; crunched the numbers; could not find any evidence of the sorts of things which they suggested might -- and they were very careful in saying "might." They didn't actually argue that there was any error in the data.

As far as the Nakagawa declaration and its alleged withholding, there's no evidence that anyone involved in the prosecution of the '528 patent was actually aware of the '928 patent. Again, everything is this -- one must have known.

THE COURT: Was actually aware of the Nakagawa declaration?

MR. MONROE: Correct.

THE COURT: I think you may have misspoken.

MR. MONROE: Oh, I'm sorry. Of the Nakagawa declaration. There's no evidence that anyone was aware of the Nakagawa declaration during the reexamination of the '528 patent.

THE REPORTER: Yes. That's different than what you said so, please,restate that again for me.

MR. MONROE: There is no evidence that anyone involved in the prosecution or reexamination of the

'528 patent was aware of the Nakagawa declaration.

THE COURT: At least consciously aware?

MR. MONROE: Or ever aware.

Dr. Oshiro was named as an inventor on that patent, but there was no evidence presented that he ever looked at the prosecution history of that patent or that he was ever involved in the preparation of the Nakagawa declaration. The most the defendants can point to is testimony from Dr. Nakagawa that he was a coworker.

THE COURT: Nakagawa was deposed but did not come to trial.

MR. MONROE: Correct.

THE COURT: But his deposition is in evidence, I guess.

MR. MONROE: Correct.

THE COURT: Okay.

MR. MONROE: And Dr. Nakagawa simply said he might have because he was my coworker, but there was no evidence he actually was involved. And Dr. Oshiro does not recall this declaration in any way.

Moreover, when you look at the declaration, the defendants focus on Mouse Jumping data and argue what that Mouse Jumping data means and say there is some correlation between that data that would lead one skilled in the art to modify the compounds, thus making it material.

We argue vigorously against this suggestion that it was material and don't believe the defendants provided sufficient evidence on that point.

As far as the knowledge, Dr. Oshiro did testify he was aware of Mouse Jumping data, but not that data. He testified he did not recall ever seeing that declaration. And other contemporaneous evidence back during that time period shows Dr. Oshiro was aware of different mouse data than what was in the declaration.

For example, his testimony about the Banno article which he authored showed -- the Banno article reports different data. Banno reports a 9.5 figure for the unsubstituted butoxy compound, which is different than that reported in the Nakagawa declaration, which was 5.5.

So Dr. Oshiro admits he was aware of Mouse Jumping data, but what he was aware of he put in the Banno article, which was a different figure. As far as -- I think that shows his lack of knowledge of that particular data the defendants are pointing to.

Finally, they argue there are allegedly false arguments during reexamination. The defendants have failed to establish that there was anything false about the statement during reexamination about the five compounds.

In context, the full section in which that statement appears makes it clear that this statement was referring to

the particular references addressing -- that were being addressed and whether those references established antipsychotic activity and discuss that property in general. As such, that statement was accurate.

And finally, the defendants try to argue a lot of inference regarding who did or did not come to trial.

With respect to Charlie Van Horn, who is the attorney that was involved in the reexamination of the '528 patent, he was identified to defendants as someone available to attend trial, and Otsuka had identified him as a potential witness. And we made it clear to the defendants that he might not appear even during trial because of a death in his family.

And based on the evidence presented, there was no reason to present him. However --

THE COURT: Could he have been deposed by the other side?

MR. MONROE: He was, in fact, deposed, Your Honor.

THE COURT: He was deposed?

MR. MONROE: And that was one of the potential issues, is whether or not deposition testimony would be needed or not. The defendants graciously offered that if we thought we needed to call him and we couldn't because of his situation, we could try to do deposition designations to have him appear.

It is noted he was someone we said would be

available, just like Dr. Oshiro and Dr. Hirose. The defendants specifically requested -- demanded that Dr. Oshiro and Dr. Hirose come to trial, and they were originally going to call them in their case. They never indicated that Charlie Van Horn had to be there. So I don't think the inference is fair.

And as far as the prosecution history, there's no evidence that Charlie Van Horn actually ever reviewed the '416 patent prosecution history. During the reexamination he was discussing the teachings of the patent itself, and there's no evidence he looked at that prosecution, and that's all speculation.

He also wasn't involved in the prosecution of the '416 patent because he wasn't even at Finnegan at the time it was prosecuted.

Finally, I tried to highlight certain issues. And there were several comments that defendants made in their openings. But I went on sort of long, Your Honor. And if I could have a moment just to address a few points.

THE COURT: You know, why don't we take a brief recess right now, and you can decide whether you want to say anything else or not. And then I'll hear the last word from you and something else from the other side.

MR. MONROE: Thank you, Your Honor.

THE COURT: Okay.

(Recess taken.)

THE COURT: Mr. Monroe.

MR. MONROE: Thank you, Your Honor.

The defendants stated that what Dr. Oshiro did was just ordinary research. And I would like to contrast that with the fact that the majority of the case, the defendants argued that the test that Dr. Oshiro used, the Stereotypy Test, was a wrong test and not a good test for establishing antipsychotic efficacy and, in fact, at one point had an inequitable conduct argument based on the fact that that test was used.

THE COURT: You mean in the history of the case, not at trial?

MR. MONROE: Correct. It's only at trial that suddenly the Stereotypy Test became an ordinary test that anybody would do.

The second point is with respect to the properties and how those properties of the compounds that we discover later might be relevant to the obviousness analysis.

I would just draw the Court's attention to In re Papesch, 315 F.2d 381 81. And in that case, the Court noted:

"From the standpoint of patent law, a compound and all of its properties are inseparable. They are one and the same."

And that has been a bedrock principle since 1963 in

looking at these sorts of issues.

As far as the double patenting issue, I would like to note, despite all of the arguments the defendants make regarding how a double patenting situation exists here, the patent office never contended that there was double patenting in view of the '416 patent, even though the patent office examined the '528 patent twice during the original prosecution and reexamination. And the patent office was vividly aware of the '416 patent during that prosecution and had that opportunity.

THE COURT: This is not a statutory theory.

MR. MONROE: That is correct, Your Honor.

THE COURT: It's a judge-made theory.

Does the patent office invoke obviousness type double patenting, to your knowledge?

MR. MONROE: Yes, Your Honor, it does.

THE COURT: And I take it that if I go back to refresh my memory, the arguments of the applicant-turned-patentee are not framed in double patenting terms. Right?

MR. MONROE: That is correct, Your Honor. The patent office did not frame the issues in that way.

THE COURT: Okay.

MR. MONROE: And on that front, I also note with respect to the P&G case which the defendants cited at the

beginning of their presentation, it's important to note that in that case there is the language they identified, but the Court's actual analysis and decision reflects that the court actually followed the analysis that we proposed.

The Court found that the invention in that case was not obvious under 35 USC 103, and in reaching that conclusion considered secondary considerations, and then when it got to double patenting said, We don't have to deal with this issue. We get to the same result that we did under 103.

So it didn't actually hit head-on the issue that the defendants would suggest, despite that it was in the decision.

THE COURT: If we do use a double patenting analysis, it is, I think, agreed between both sides that under that type of analysis you look at the state of the art as of the date, in this case, the '528 patent, or not?

MR. MONROE: You do, Your Honor.

THE COURT: You're only comparing the claims of the '528 and the '416, but you're looking at the state of the art?

MR. MONROE: Yes. Plus, the state of the art in the context of this case is the '416 patent itself. So you can use the specification of the '416 patent and other claims in that patent to interpret the claim in the '416 patent in which they focus because that patent actually is in the prior

art and becomes part of that prior art.

THE COURT: True. But would something like the -- those -- something like the Banno article be in the prior art for the '528 patent?

I'm not sure I want the Banno article. Let's use the ones you have immediately handy. You know, the 1977 and early '78 literature and the Wise poster would be in the prior art because if it is prior art at all, it's 1987. Right?

MR. MONROE: Correct.

THE COURT: So obviousness type double patenting, you still look at the state of the art as of the application date for the later patent, the '528 patent. You don't confine it to the state of the art as of maybe when the '416 was applied?

MR. MONROE: That's correct. I understand. Yes, Your Honor, that's correct. You go to the date of the filing of the application of the claim which is being reviewed for patentability. That's correct.

Two more points. With respect to Charlie Van Horn, we would also like to note he was deposed, as discussed, and during his deposition the defendants did not ask the questions regarding the Nakagawa declaration. We did not even provide him with a copy of that during his deposition.

So as a practical matter, with respect to the

inference, the defendants never pursued that issue with Mr. Van Horn prior to trial.

Finally, there were a lot of statements by counsel that lots of things were unrebutted. And we would just ask that the Court look to the proposed findings to see if any of those things were rebutted.

They may say the same thing about my comments about things that are not in dispute, but I think it's important to take at face value what's being said.

And I would like to correct one issue. Your Honor, you asked about the compound D and E in the Nakagawa declaration, whether or not those --

THE COURT: All the lettered compounds in that one test that we're focusing on.

MR. MONROE: I do not have with me my cheat sheet, and I answered incorrectly. They were carbostyrils, Your Honor.

That's all. Thank you, Your Honor.

THE COURT: Ms. Holland.

MS. HOLLAND: I want to first address the issue -- the question that you posed about whether this is a case where the double patenting voucher can apply. And the answer is absolutely yes.

And just sitting in my chair, I thought of three cases in which the patents-at-issue, the double patenting

references, were completely separate patent families.

THE COURT: And they're cited in your papers anyway?

MS. HOLLAND: The cases are cited, but I want to make sure that Your Honor is looking at them in that context.

THE COURT: Okay.

MS. HOLLAND: The Proctor & Gamble case that I had up on the screen this morning, the Federal Circuit 2009 decision, that was a case where the patents were from separate families.

The Sun vs. Lilly case, which is a 2010 Federal Circuit case, the patent and the double patenting reference were from completely separate patent families.

And then there's the In re Berg case which is cited in our posttrial papers. And there is a -- there's a footnote in that case that makes it clear where it says that the applications that are being discussed there are not related as by continuation, in part or divisional, and neither references the other.

And all those cases are cited in our brief. I'm not sure they're cited for that point, but they're all found in the briefing.

THE COURT: Thank you.

MS. HOLLAND: I think Mr. Monroe started -- or at least it was near the beginning of his presentation when he said that Otsuka had to go back to the drawing board. That's

simply not the case, and I think it's an important issue here because it impacts inequitable conduct in addition to obviousness.

When Otsuka decided that it was going to look at something next generation to OPC-4392, one of the first things it did was test the 2,3-dichloropropoxy.

If you recall, Your Honor, Dr. Oshiro testified at trial that his idea was they wanted to get a compound whose activity in the Anti-Apomorphine Stereotypy Test was better than chlorpromazine. That was the goal.

And the evidence at trial showed that they tested the 2,3-dichloropropoxy compound, and it was better than chlorpromazine. It fit the profile Otsuka was looking for to commercialize an antischizophrenic drug.

Why didn't they put a 2,3-dichloropropoxy on the market? That question was also answered by Dr. Oshiro. There is an e-mail that's in evidence from Dr. Oshiro to Dr. Hirose where he states that the patent term on an OPC-4392 series compound, in other words, 2,3-dichloropropoxy, which was part of that series, was insufficient.

And Dr. Oshiro also testified that there was a policy at Otsuka at the time that they would not commercialize anything unless they could get sufficient patent protection on it.

So the 2,3-dichloropropoxy, not only did Dr. Oshiro know that it tested better than it tested in the Hirose declaration; it was a compound that actually fit the profile that Dr. Oshiro was looking for.

And that was off the bat, Your Honor. They could have gone to market with that compound. They didn't want to because they couldn't get another patent on it.

Mr. Monroe also made a point of saying that the three asserted claims at issue in this case have to be analyzed separately. And in fact, Dr. Press did analyze each of those three claims separately.

If we can look at page 141 to 142 of the trial transcript. Can we blow up from line 11 on page 141, or highlight -- circle that. Thanks.

As you can see, Dr. Press was specifically asked not only about Claim 12, but about Claim 17.

And if we can go to the next page.

He was also asked about Claim 23, starting from the middle of that page. And Dr. Press explained why all three of the asserted claims at issue in this case are obvious variants of the unsubstituted butoxy.

Can we go back, and starting from line 15 on page 142.

This is from Dr. Press' testimony. Common sense, Your Honor. It's obvious. If you know that aripiprazole has

antipsychotic activity and that it was going to be formulated into a dose that could be used to treat schizophrenia, of course you would want to use that agent to treat schizophrenia in a patient.

That's Claim 23 of the '528 patent, the asserted claim that talks about the method of treatment.

Dr. Press' testimony was that you would know aripiprazole would be an improved antipsychotic agent, so of course you would want to use that drug to treat patients. That's the whole point of the research.

Just staying on the topic of Dr. Press for one second. Mr. Monroe was talking about Dr. Press' credentials. And I just want to remind the Court of Dr. Press' testimony at trial, that he was the only expert in this case who was actually sitting in a lab trying to develop antischizophrenic agents at the relevant time frame.

Mr. Monroe disparaged that by saying it was 25 years ago, but that's the right time frame in this case. He was actually in the lab doing his work at the right time frame.

Not only was he in the lab trying to develop an antischizophrenic agent; he actually did come up with one. He testified at trial that while he was at Lederle Labs, he had synthesized the compound olanzapine that's currently being marketed by Eli Lilly.

The issue there, as Dr. Press testified, was that he

at Lederle and Eli Lilly were working on it at the same time, unbeknownst to each other, and that there was an interference, and ultimately, Eli Lilly prevailed.

But Dr. Press actually did develop an antischizophrenic agent that is currently being marketed today.

Mr. Monroe made the point that chlorination is not required for a compound to have antischizophrenic activity. And of course that's the case, Your Honor. Defendants are not saying that in every case you would need a chlorine in a molecule in order to have antischizophrenic activity.

What we're looking at here are not generalizations. We're looking at a very specific reference, the Nakagawa declaration, that has very specific teachings about chlorine and how they would affect the unsubstituted butoxy. It says put chlorine at the 2-position. Put chlorine at the 3-position. Don't put chlorine at the 4-position.

So although you may not generally need -- or chlorine may not always be required, in this particular case the prior art is very clear that chlorine at the 2- and the 3-position will improve antipsychotic activity.

Mr. Monroe also brought up the fact that defendants didn't actually -- or Dr. Press didn't actually test any of the compounds in the prior art to see how they would actually perform.

But of course, that is not the analysis that you're supposed to do on obviousness or on double patenting. You're supposed to only be looking at what the person of ordinary skill in the art would know from the public literature at the time.

Any testing that any expert would do in 2010 would be completely irrelevant to what the person of ordinary skill in the art would know based on the publicly available literature as of the right date.

That's all I have, Your Honor, but I think Mr. Feldman has something to say.

THE COURT: That's fine.

MR. FELDMAN: Just very briefly, Mr. Monroe discussed Dr. Roth's testimony about certain red flags that he saw with OPC-4392, including the notion that it was an activating agent.

Our point on this, as brought out in the briefs, is that Mr. Monroe and Dr. Roth weren't fairly really treating those articles in terms of what they were actually teaching. In other words, Dr. Roth's conclusions weren't really consistent with what Otsuka and Dr. Murasaki were saying at the time.

For example, they point to a 1988 Murasaki article. Although it's dated 1988, which makes it seem later, it's actually in English, and I think it's talking about an

earlier Phase I study. Dr. Roth said that's a red flag.

And if you recall on cross-examination, the actual conclusion of that particular paper, which is PTX-545 at 802 -- and the transcript page is at 1405, starting at line 9 -- what they actually concluded was that, in fact, this compound was safe enough and should progress.

And in fact, it did. OPC-4392 progressed from Phase I to Phase II and ultimately to Phase III clinical trials.

So Dr. Roth's interpretation of OPC-4392 really is not consistent with what the literature says or taught about it.

The plaintiffs also brought up several sort of after-developed or after-appreciated features of aripiprazole.

Our point on that is that it doesn't really distinguish the prior art carbostyril compounds because there's nothing to show that the prior art carbostyril compounds didn't also have those sorts of properties.

And in fact, in some cases there were instances where there was literature teaching that the carbostyrils in the prior art did have those features.

For example, they talked about having presynaptic agonism and postsynaptic antagonism behavior. There was literature that we discussed at trial and is in our briefs,

DTX-104, for example, that shows that, in fact, OPC-4392 was characterized as having those same sorts of properties.

And I'll also remind the Court that in the '416 patent specification, again, there was a whole host of CNS activities that were discussed in there.

And so the fact that Otsuka then decided to test and get FDA approval on various other CNS-like indications is really consistent with what the '416 patent was already teaching in terms of the types of activities that these carbostyril compounds would be expected to have.

And finally, Your Honor, again, they've brought up the heat map and this notion of antihistamines with respect to the '416 patent.

And the trial testimony, I believe, and again, this is highlighted in our briefs, showed that just because something had some antihistaminic activity did not preclude it from being an antischizophrenic drug.

And in fact, just the opposite, as Dr. Press testified, I believe. Many antischizophrenic drugs, in fact, show some activity at that receptor.

And I believe that's corroborated by Dr. Roth's heat map that show that a lot of the marketed antischizophrenic drugs, in fact, were active at that particular receptor.

And one final point, Your Honor. The Banno article that they keep referring to was not prior art, so it doesn't

really count in terms of analysis.

Thank you, Your Honor.

THE COURT: That's why I took back that --

MR. FELDMAN: Great. Understood.

THE COURT: All right. We will get you a decision as soon as we possibly can. We appreciate very much all the work that's reflected in the posttrial submissions and also your very, I think, well-organized presentations today, both sides.

There's 600 pages of posttrial briefing, something like that. And I will take the liberty of referring to chunks of the record by referring to inclusive pages of your posttrial submissions just in order to get an opinion out.

But when you see us do that, that will signify to you that you have all of your arguments full text available to take with you as this case progresses through the Courts, and that we've considered them, and that we're referring to the whole body of whatever the portion is to which we're referring in making our evaluation.

And we will call you up before we release anything. You will know. And we'll figure out a timetable for releasing it. We'll figure that out with you.

And some of your materials have been "filed under seal." Some of them haven't made it onto the docket in any form at all, these posttrial submissions as of yesterday,

which is fine. I have them in chambers. If you want to actually get them filed, you have to get them filed under seal. And the magistrate judge can do the order for you to get that much of it done.

And then probably our opinion will be initially filed under seal so that we can get it to you. We may e-mail it to you first so that you can decide whether you want it filed under seal or not. All of these are options. But I assure you that we will not put an opinion on the docket without consulting you first. Okay?

MS. HOLLAND: Just one more thing that I want to put on the record, Your Honor. We're going to be submitting our deposition designations formally today. I just wanted to have that on the record before the record is closed.

THE COURT: Fine. Do you need us to be in session to do that?

MS. HOLLAND: I don't believe so. I just wanted it to be put on the record that we were putting that in before the close of this.

THE COURT: Is that agreeable to both sides?

MR. MONROE: Yes. We're doing the same.

THE COURT: Yes. And so are you going to submit a copy to chambers?

MS. HOLLAND: Yes. Would you like a copy, Your Honor? However Your Honor prefers.

THE COURT: Well, for us to have our bench documents complete, it would be good if we get something.

Now, the designations may just designate pages and lines, right, or will they actually show the text of the testimony?

MS. HOLLAND: We can do it whatever way will be easier for the Court. I think currently we have page and line, but we can --

MR. MONROE: I thought we were doing excerpts.

THE COURT: So it will be readable?

MS. HOLLAND: Yes, yes.

THE COURT: Okay. That's fine.

MR. FELDMAN: Also, I believe -- are there any exhibits that go with the depositions? There may be a couple of additional exhibits that are supported by the designations, and we'd like to move those into evidence as necessary.

THE COURT: You can attach them to the deposition designation. That would make it the easiest way to refer to them when reading.

MR. MONROE: I guess we would like an opportunity to know which ones in case we have an objection.

MR. FELDMAN: Right. Understood.

THE COURT: Okay. And if you have any problems, of course, we're available. Otherwise, if you don't, you can

just submit these as part of the record. Let the court reporter know how you're marking this so the transcript can reflect that it's been received into evidence.

All right. Anything else?

Do we stand adjourned?

Thank you very much.

(Proceedings adjourned at 1:33 p.m.)

CERTIFICATE

STATE OF NEW JERSEY)
) ss:
COUNTY OF MERCER)

I, JOMANNA DeROSA, a Certified Shorthand Reporter and Notary Public within and for the States of New York, New Jersey, California and Arizona, do hereby certify that within is a true and accurate transcript of the proceedings held on October 21, 2010.

I further certify that I am not related to any of the parties to this action by blood or marriage, and that I am in no way interested in the outcome of this matter.

In witness whereof, I have hereunto set my hand this 21st day of October, 2010.

s/ JOMANNA DeROSA

I N D E X